ENDOTOXIC SHOCK

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For Reference

NOT TO BE TAKEN FROM THIS ROOM

THE UNIVERSITY OF ALBERTA

ENDOTOXIC SHOCK:
OBSERVATIONS ON PATHOGENESIS AND TREATMENT

by

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A THESIS

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The undersigned certify that they have read, and
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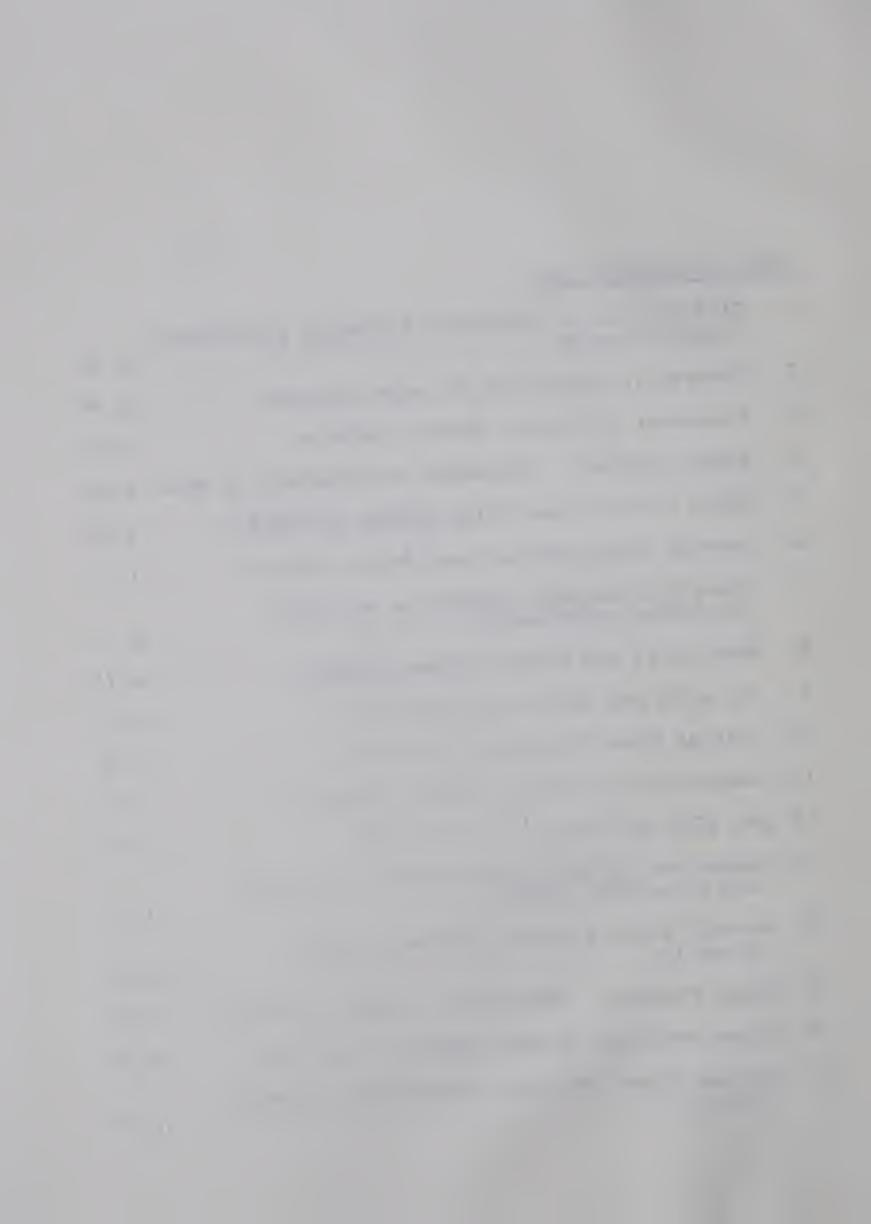
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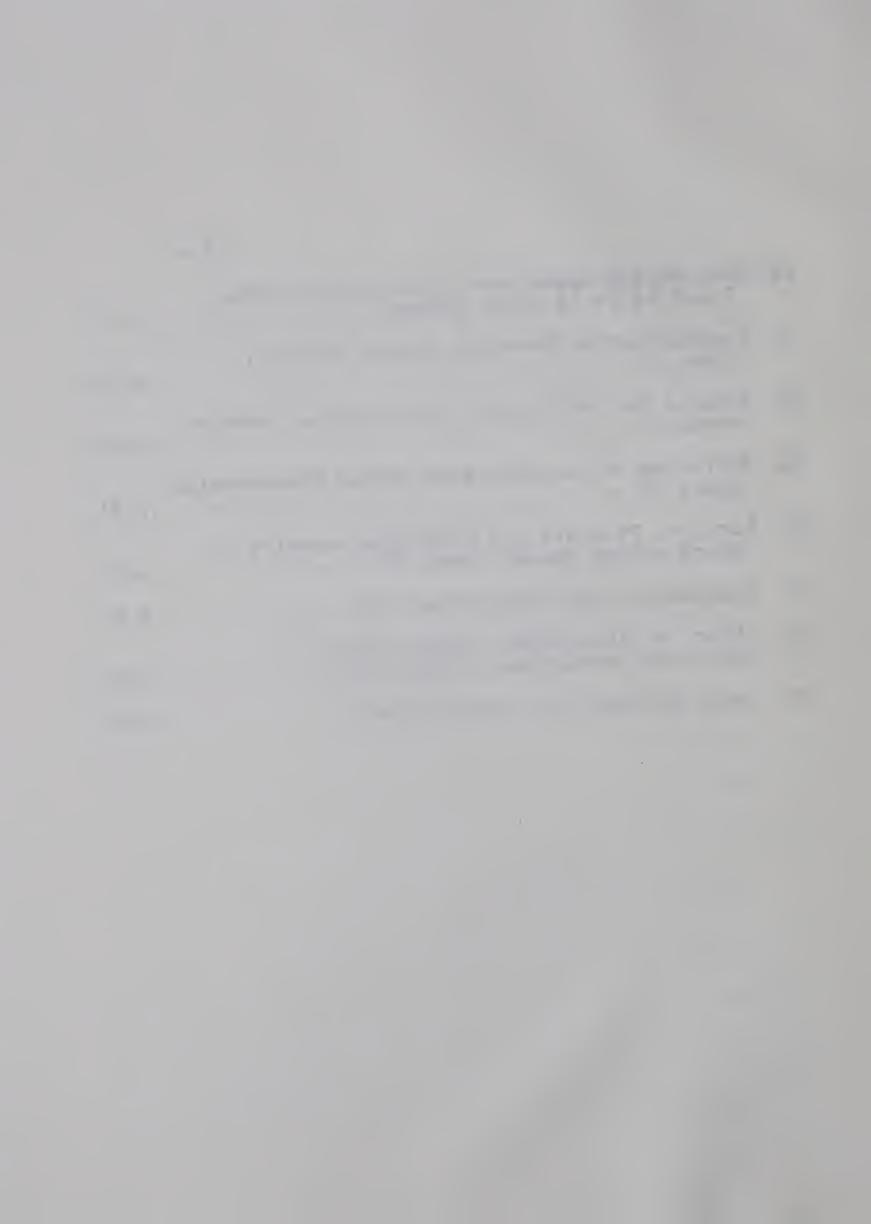The Canadian Life Insurance Officers Association for a Fellowship.

LIST OF ILLUSTRATIONS

ABSTRACT:

In the past fifteen years a syndrome of shock associated with an <u>Escherichia coli</u> bacteremia has been recognized and carefully studied in patients.[7] Experimental models for the study of this problem have been developed and a greater understanding of the patho-physiological changes associated with this clinical condition has been evolved.[19,61]

It was demonstrated early in the investigation of this problem that the toxicity of the bacteria was related to the presence of a specific endotoxin found in the bacterial cell wall.[12] The precise mechanism by which endotoxin produces its effects is still incompletely understood.[61,62]

Once the clinical syndrome became well known, various methods of treatment were evaluated. It was found that, in spite of good supportive care, thirty to eighty percent of all patients developing endotoxin shock would die.[1,2,3,4,5,6,7]

This study investigates the pattern of peripheral blood pressure changes during shock in the normal dog and in the dog with a porto-caval shunt. In both groups of animals there are marked changes in blood pressure but a significant

difference exists between the pattern of change in the two groups. The normal animals had an initial rapid drop in blood pressure in response to endotoxin, a partial recovery which was sustained for hours and a terminal, steadily advancing hypotension.

The porto-caval shunt animals demonstrated a more gradual initial drop in blood pressure with stabilization at a new level and terminal hypertension. The porto-caval shunt, therefore, prevented the portal congestion (which has been well documented in dogs.[31,32,33]) The circulatory changes in these animals are noted to resemble more closely those of the human being during endotoxin shock.[24,51]

The blood pressures in the marrow cavity of the femur were recorded both in normal dogs and in dogs with porto-caval shunts. The changes in the marrow cavity pressures suggested that vascular constriction was occurring during shock. There was further evidence that this constriction was progressive and showed no spontaneous tendency to resolve.

The buffering mechanisms of the blood as reflected in changes of pH, pCO_2 and total CO_2 were studies both during shock and following efforts at therapeutic reversal of shock. The serum lactate and pyruvate were also measured during shock and after therapy. Metabolic acidosis was found to develop progressively as the shock persisted. The magnitude of the acidosis was found to be greater than previously reported.[63] By restoring the circulation to normal and mobilization of the products of anaerobic metabolism, an estimation of the total peripheral acidosis could be made. This information was utilized therapeutically; the pH and pCO_2 were titrated to a physiologically acceptable level with sodium bicarbonate.

Observations were made on the alterations in the fibrinolytic system during profound shock. In agreement with the work of others the presence of excess fibrinolytic activity and a hemorrhagic tendency in the shocked animal was noted.[64]

A treatment program was instituted which attempted to restore the abnormalities noted to normal. This program consisted in its final evolution of the use of an adrenergic

blocking drug, phenoxybenzamine, to aleviate the peripheral
vasoconstriction and the simultaneous administration of a
plasma volume expander to compensate for the temporary
increase in vascular volume brought about by the drug
administration. Sodium bicarbonate was administered to
buffer the acid metabolites which were mobilized from
peripheral tissues. Epsilon amino caproic acid was used to
prevent excess fibrinolytic activity and therefore prevent
the bleeding tendency which the animals otherwise exhibited.
Glucose, electrolyte solutions and antibiotics were also
given intravenously as supportive therapy.

An animal was considered to be successfully resuscitated
if a return of the blood pressure to a normal level was
accomplished and maintained, if urinary output returned, if
bleeding from the gastro-intestinal tract was controlled and
if the pH, pCO_2 and total CO_2 were all restored to a normal
level. In addition the animals' mucous membranes and paw
color were noted to return from a cyanotic color with poor
capillary filling to a normal, well oxygenated appearance
with rapid capillary filling.

These changes had to be maintained for 48 hours to meet

the criterion of permanent resuscitation. This therapy
was evaluated in a group of animals which had experienced
prolonged shock. The treatment course was found to
successfully resuscitate terminally ill animals.

INTRODUCTION:

"First, let me enter a plea for a larger conception
of disease processes. 'No treatment without diagnosis',
is a truism for the educated practitioner. But is giving
a name a diagnosis? Does even a thorough knowledge of the
anatomical lesions of pneumonia explain the fever, the
rapid pulse, the delirium? No more than a study of the
anatomy of the lung elucidates the physiology of respiration.
What does the autopsy tell of the tremendous chemical
disturbances of diabetes? Anatomical pictures, normal and
pathological, are the indispensable foundation; but every
medical man must learn to think in physiological terms, if
he is to have any conception of those intricate disturbances
of function, which are the chief manifestations of disease.
This is especially true of the more dangerous symptoms
which arise, and which must be combated, if life is to be
saved. Yet how seldom can we obtain a satisfactory des-
cription of the mode of death in a given case. In the
hospital it is exceptional when any house staff can answer
a question on this point. It is fundamental to treatment
that we should know whether death may come through failure

of the heart muscle to maintain the circulation or from
gradual paralysis of the respiratory center, from oedema
of the lungs or oedema of the glottis, from internal
haemorrhage or surgical shock. Let us, therefore, as
clinicians be students of pathological physiology, and
carry our thoroughness into our symptomatic treatment.
Then our by-word shall be, 'no rational symptomatic
treatment without adequate physiological concepts'."

<div align="right">Theodore C. Janeway, 1907[8]</div>

Shock in association with infection has been observed
and recorded for many years. There was a delay however,
in recognizing that bacterial products could produce
shock directly, apparently unrelated to specific organ
damage or fluid and electrolyte losses. The investigation
of the pathogenesis of this shock and its treatment have
all been of recent origin.

A sufficient number of experimental and clinical in-
vestigations have now been published to allow consideration
of endotoxic shock as a unique entity and attention will
be directed in this discussion only to reports dealing with
this type of shock. Basic similarities to, or differences

from, other types of shock will be mentioned only to
clarify the basic physiological changes which occur.

DEFINITION:

Shock is a persistent alteration in the circulation which results in an insufficient perfusion of many or all of the tissues of the body. This insufficient perfusion is demonstrated primarily as an oxygen deficit in comparison to the needs of the tissues for aerobic metabolism. To a less degree, there is interference with the carbon dioxide transport and the supply of metabolites to the tissues. Should this diminished perfusion continue, the death of individual tissues, and finally of the organism, would result.

Shock is not associated with any specific blood pressure, pulse rate or cardiac output although each of these may be used to help evaluate the degree of shock clinically and to describe the progression of the patient's vascular reactions.

Endotoxic shock is a type of diminished tissue perfusion which is initiated by the introduction into the individual's circulation of a lipopolysaccharide toxin. This toxin is found in the capsule of certain gram negative organisms.[9,10] The similarities which exist

between shock produced during infections with different
gram negative organism strongly suggests that the mechanism
through which shock develops in each one is similar.[9,10,11,12]

However, for clarity, consideration has been limited
to the manifestations of shock which are associated with
an <u>Escherichia</u> <u>coli</u> (<u>E</u>. <u>coli</u>) infection. Reference will
be made to the similarities which occur when infection is
caused by other organisms.

HISTORICAL REVIEW:

In 1907 Janeway discussed the association of vascular
failure and sudden death in a patient who had lobar
pneumonia.[8] He went on to discuss the common thought
which existed at that time that these patients had died
of "heart failure." But he introduced some clinical
observations that strongly suggested that the peripheral
vasculature was at prime fault and that the heart was
able to maintain a normal pumping activity until the
very terminal state. In this article he also presented
the experimental work of Rhonberg and Passler which was
published in 1899.[13] These investigators had injected
pneumococcus, pseudomonas and diptheria organisms intra-
venously into rabbits and had observed a drop in blood
pressure and signs of vascular failure. But in these
animals no deficiency of the cardiac activity was detected.
These are two of the earliest accounts relating infection
to the subsequent development of hypotension and death.

In 1924 a report of twenty-eight cases of bacteremia
due to E. coli was published.[1] Three cases were terminal
invasions of the blood in patients with a severe systemic

disease. Of the twenty-five other cases, eight patients died. In only one of the reported cases was hypotension prior to death described, and no special emphasis was given to this occurrence. The clinical picture of a patient with E. coli bacteremia was vividly described.[1]

A similar report of eighty-two cases of bacteremia appeared in 1929.[2] Forty percent of these cases were E. coli on culture. Eleven of the fifteen fatalities recorded, in this study were associated with gram-negative organisms. In four of these eleven fatalities hypotension was recorded, but this was not recognized as being caused by the infection, per se.[2]

Eight cases of shock associated with infection (all gram-positive cocci) were reported in 1941 by Ebert and Stead.[14] They recognized that the infection precipitated the circulatory changes and speculated that therapy should be directed at clearing the infection, since support of the circulation by various methods appeared to be ineffective. They also felt, on clinical grounds, that the patients were all normovolemic, and that the circulatory disturbance consisted of peripheral vascular

pooling, secondary to abnormal nervous adjustment of the peripheral vascular bed.[14]

In the year 1944, Aub [15,16,17] published the results of extensive investigations into the mechanisms of production of hypotension and death, following shock produced by prolonged ischemia in the hind legs of dogs ("tourniquet shock"). These investigators were able to show a high incidence of infection with pathogenic bacteria in the traumatized limbs.[16,17] All of the muscle exudates which were investigated following tourniquet shock were found to be infected;[16] seventy percent of the infection was caused by Clostridium perfringens.[17] Culture of the clostridium and re-injection into the animal produced hypotension and shock which was similar in many respects to that produced by the tourniquet shock itself.

These investigators also related the toxicity of the fluid to the number of organisms present in the exudate of the animal's hind limb. They concluded that the toxic factor in traumatic shock in dogs was related to infection.[15,17]

The first experimental report, relating the development

of shock and death to the toxins of gram-negative bacteria,

was published in 1944.[11] The injection of the purified

Shiga toxin resulted in a clinical picture in dogs which

is similar in most respects to that seen with E. coli.

They related the hypotension and the drop in cardiac out-

put, which they recorded, to a poor venous return. There

was a consistently low central venous pressure. The

circulating plasma volume was normal in one-third of their

animals, and there was variable hemoconcentration in the

other two-thirds.[11]

By 1945 the concept of hypotension caused by infection

and not responsive to the usual forms of therapy had be-

come established in the literature.[20,21,22] It was pointed

out in a review of shock associated with war injuries,

that sometimes the hypotension did not respond to volume

replacement, and one of the causes for this was associated

infection (particularly peritonitis).[21]

Waisbren, in 1951, made an outstanding contribution

to the understanding of the clinical manifestations of an

E. coli infection.[3] He observed that there were two general

clinical pictures associated with bacteremia. One, the
"toxic" state, was of a warm, flushed individual with
rapid, bounding pulse and fever. The other was of a cool,
moist individual, hypotensive, apprehensive and restless,
which he designated the "shock-like" state. This second
group contained fifty percent of his cases.

   Of the five deaths in his series of twenty-nine cases,
four occured in the "shock-like" group of patients. This
author was the first to emphasize the existence of a
definite clinical syndrome of shock associated with gram-
negative sepsis.[3]

   In 1951 the clinical picture of a pure endotoxemia
caused by gram-negative bacilli was presented in a report
of fatal transfusion reactions due to contamination of the
blood with bacteria.[23] These investigators also suggested
on clinical grounds that there was no significant reduction
in blood volume associated with the hypotension. They
speculated that there were "injurious effects----on the
peripheral bed".[23]

   By the middle 1950's a number of papers dealing with

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the clinical aspects of bacteremic shock had appeared. [4,5,6,7,24,25,26,27,28,29] A large portion of these re-
ported cases were caused by the coli-aerogenes group of
bacteria. [4,5,6,7,23,24,27,28,29]

Initially, little more than descriptive facts were
added to the knowledge of this clinical entity. It be-
came obvious in reviewing large numbers of cases that
approximately fifty percent of all cases died irrespective
of good supportive therapy such as antibiotics, blood
transfusions, fluid and electrolyte correction, - com-
bined with surgical removal of the infected foci where
applicable. [3,4,5,6,7,23,29]

A considerable amount of interest had developed in
this clinical entity, however, and largely through the
efforts of Spink, a purified preparation of E. coli endo-
toxin became available for experimental purposes. [10,30]
With this purified endotoxin and the use of larger mammals
(primarily the dog) a number of controlled experiments
were performed. These experiments helped to clarify the
significance of any changes which had been previously
noted. They also allowed more intensive investigation of

the vascular reaction which occur during shock.[18,19,30,31,32]

NATURE OF THE TOXIN:

ORIGIN: The endotoxin of <u>E. coli</u> is located in the
cell wall of this species. It is normally released only
on the death of the bacteria.[12] It can be extracted
from the cell wall by several organic solvents, with-
out destroying the microscopic continuity or the staining
property of the cell wall. Of these organic solvents
the most common is very dilute trichloroacetic acid.[9,12]

CLINICAL SOURCE: The endotoxin of <u>E. coli</u> occurs as
a clinical problem only when the bacteria are present in
the blood stream in large numbers or are multiplying in
tissues.[1] Familiar examples in clinical medicine include
the bacteremia following the transfusion of infected
blood;[23,66] urinary tract operations or obstruction in
the presence of infected urine;[44,67] septic abortion;[45,65]
terminal illness as in leukemia, lymphoma or carcinoma;[1]
ascending cholangitis;[46] intestinal obstruction[27,47] or
infarction of a loop of bowel.[27,48] The endotoxin
manufactured by the normal coliform inhabitants of the
bowel is either destroyed by the intestinal tract, is
not absorbed through normal mucosa, or, whatever amount

is absorbed, is detoxified by the reticulo-endothelial
system of the liver.[68,69] The endotoxin of E. coli is
similar chemically, antigenically, and physiologically
to the endotoxins isolated from a large number of gram-
negative bacteria, a few gram-positive bacteria and some
plant sources.[9,12]

CHEMICAL NATURE: The purified endotoxin give chemical
reactions for lipid and polysaccharides. The lipid is
not extractable, however. This endotoxin is heat and
cold stable but tends to lose its potency on storage.
On hydrolysis with warm acetic acid or cold alkali, it
is found that the toxin complex has the following general
components:

> 55 - 60% - polysaccharide
>
> 17 - 20% - protein
>
> 9 - 12% - lipid   [9,12]

The polysaccharide varies from species to species
of bacteria but usually consists of a hexosamine such as
n-acetylglucosamine, d-glucose, d-galactose and usually
l-rhamnose with other sugars in small amounts. The
compound also contains 1% phosphorous.[9,12]

The lipid content is made up of palmitic acid, oleic acid and alpha-glycerophosphoric acid and a nitrogenous component. The protein consists of three distinct protein groups which can be separated antigenically. The toxicity of the compound is attributable to a small component which remains attached to the polysaccharide or to the protein on hydrolysis. This component is high in carbon and phosphorous.[9,12]

The toxin varies in the same bacterial species as to antigenicity. Some toxins produce fever and no shock where as others produce shock and no temperature elevations.[9, 12]

MODERATE UPTAKE: Spleen, Bone
SLIGHT UPTAKE: Intestine, Muscle, Heart
NO UPTAKE: Erythrocytes, Brain

● PLASMA
◉ LIVER
▲ BUFFY COAT
☆ LUNG
✡ KIDNEY

TOTAL RADIOACTIVITY INJECTED

TIME IN HOURS

REDRAWN FROM: BRAUDE, A. I. CAREY, F. J. and ZALESKY (Reference 18.)

FIGURE 1

EFFECT OF THE TOXIN:

ADMINISTRATION: Endotoxin is effective in the same
dose range when administered intravenously or intra-
peritoneally and produces the same clinical picture.[18]
As would be expected, the endotoxin is not effective
orally.[68,69] In studies using endotoxin which has been
tagged with chromium 51, it has been shown that the
endotoxin is quickly cleared from the blood stream,
reaching high concentration first in the "buffy" coat
layer of the blood and then being found largely in the
liver, spleen and lungs.[18] (Figure 1). None of the
tagged toxin is detectible in the brain. Plasma levels
dropped to three-quarters of the starting level within
an hour and down to one-half of this level by the end
of two hours. Stimulation or depression of the reticulo-
endothelial system prior to the injection of toxin results,
respectively,[18] in the acceleration or depression of the
rate of endotoxin clearance.

OBSERVATIONS DURING SHOCK IN THE EXPERIMENTAL ANIMAL:

GENERAL REACTIONS: In the unanesthetized dog, following intravenous injection of endotoxin, the following events occur. At first, the animal appears to be very apprehensive. He may struggle violently in his harness. He develops a tachypnea; intensive salivation and lacrimation occur: the animal has episodes of shivering and perhaps a running, restless motion of the legs. Vomiting occurs soon thereafter and, following the initial vomiting, the animal may continue to retch for some time. Micturition frequently occurs at this time also. Within a brief period the animal becomes quieter and only the tachypnea, lacrimation and salivation persist.[31] A subconjunctival edema occurs in a large percentage of animals.

Within 30 to 40 minutes diarrhea appears. This will at first be only normal diarrheic stools, but with the progression of time, segments of mucosal tissue are passed in the stool, along with large quantities of fluid and blood. The animal develops ataxia, a dragging of the hind limbs, and in the later stages, apathy, stupor and coma. At intervals during the shock period the animal will struggle

violently for a few minutes as if attempting to escape.[31]

The animal's rectal temperature may rise a few degrees within the first few hours but frequently stays within normal range. Death occurs in from one to twenty hours, usually within twelve hours following the initiation of shock. The terminal event usually sees the respiration ceasing before the heart beat stops, and terminally, the animal has tonic and clonic convulsions.[9,31,43]

In addition to these dramatic clinical events, it is also possible to observe that the mucous membranes of the animal become quite dusky during shock. Depression of the tongue or forepaw reveals a very slow return of color, suggesting a delayed capillary-filling pressure. In occasional animals edema of the forepaws or of the loose, subcutaneous skin over the back is observed during the shock state.[70]
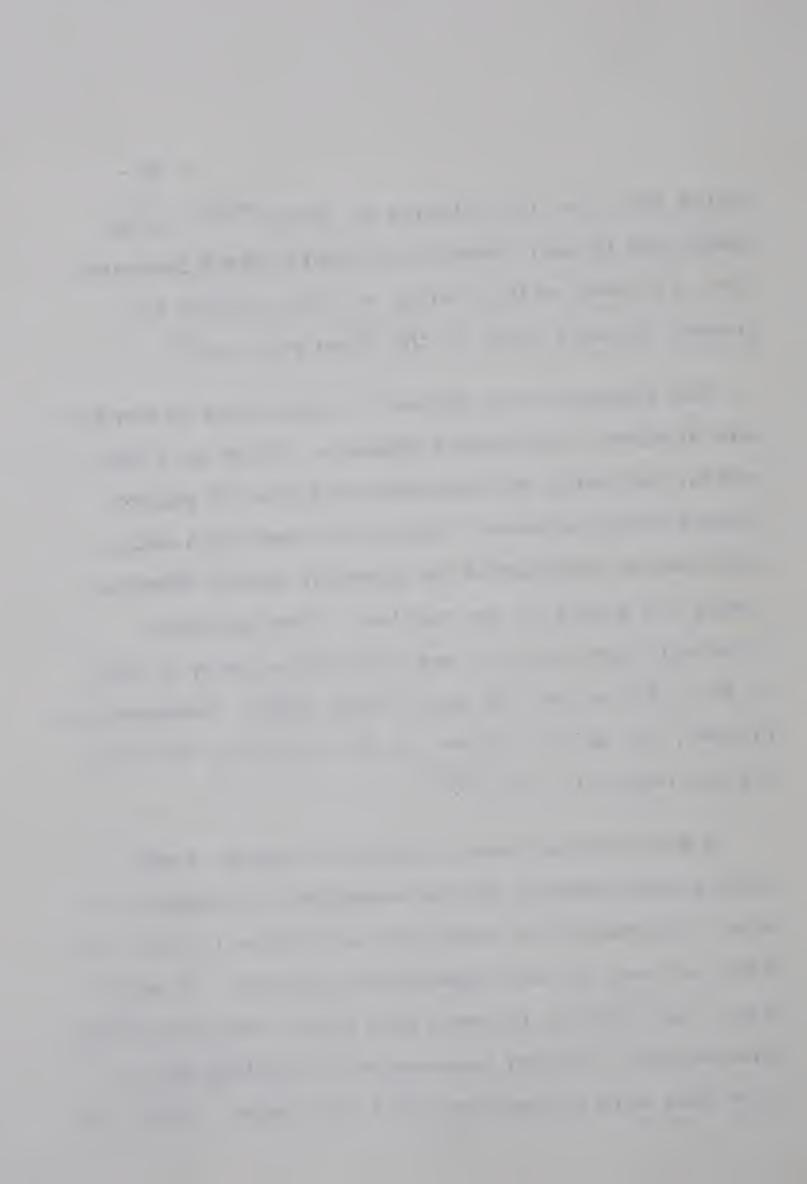
The reactions of other large mammals in shock are similar, with the following exceptions; in the cat, marked hyperpnea and dyspnea are prominent early symptoms and some cats die of acute pulmonary edema and bronchospasm

during the first five minutes of shock.[49,50] In the
monkey and in man, there is an initial blood pressure
rise, followed, within thirty to sixty minutes by a
gradual downward drift of the blood pressure.[51]

The syndrome of shock due to endotoxemia in man is
very distinct and deserves emphasis. There is a lag
period, following the injection of toxin, of approx-
imately thirty minutes. This is followed by a chill,
which may be accompanied by diarrhea, severe abdominal
cramps and aching of the muscles. Blood pressure
(diastolic and systolic) may rise initially by as much
as 60 to 180 mm Hg, the pulse being rapid. Leukopenia is
present, and within fifteen to thirty minutes the temp-
erature begins to rise.[45,51]

In more serious cases, cyanosis, shallow, rapid
respirations, changes in the sensorium and oliguria de-
velop. Gradually the blood pressure begins to fall, and,
within an hour or two, hypotension develops. In milder
cases, the chill is followed by a flush phase and gradual
defervescence. During hypotension the patient may at
first have warm extremities and a full pulse. Later, in

severe cases, the pulse may be weak or not palpable and the extremities cold. The skin is ashen-grey, moist and cool; there is mottled cyanosis.[24,51]

The human survives longer than other animals in shock, but death usually occurs between twelve and ninety-six hours after the onset of hypotension.[45,51]

HEMODYNAMIC EFFECTS:

Following intravenous endotoxin administration in the dog, there is a delay of thirty seconds to one minute and the blood pressure drops. The initial drop is quite marked, reaching a level of 40 to 60 mm of Hg. The pulse pressure also narrows.[33,57] The pulse rate increases. From this low point, the blood pressure gradually rises, until it reaches 75 to 100 percent of its pre-endotoxin level in approximately 10 minutes. Then the blood pressure gradually declines until the animal expires after a period of several hours.[32,33]

The initial drop in blood pressure in the dog has been shown to be due to a markedly diminished venous return. This diminished venous return decreases right heart filling pressure and consequently depresses cardiac output. Weil and associates found that the cardiac output in four dogs which were in endotoxic shock fell from control levels of 113,240,180 and 156 ml/min. to 43,50,97 and 51 ml/min. respectively. This fall was associated with a slight rise in total peripheral resistance in the cases of three of the four animals. The drop in blood pressure was not due, therefore, to peripheral

dilatation of the resistance vessels.[31,32,33]

In another experiment in which constant venous return was supplied to the heart from an external blood reservoir, the blood pressure and cardiac output did not fall but the venous return was remarkably depressed.[33]

It is instructive therefore, to consider in detail the changes which have been observed in the peripheral vessels. It has been shown by observing conjunctival vessels, mesenteric vessels, rabbit ear vessels and skin vessels that the following sequence of events occurs. Following endotoxin injection, there is spasm of the smaller arteries and arterioles (resistance vessels); there is also spasm of the smaller veins and venules (capacitance vessels). This is not an all-or-none reaction but occurs spasmodically along the vessels with both contraction and relaxation occurring in different vascular beds or along a single vessel at the same time. However, the relaxation phase becomes increasingly brief and, consequently, perfusion of the tissues decreases.[31,52]

The arteriole, after a period of constriction, then dilates again and remains dilated. The venule, remains constricted for a longer period. This leads to an increased perfusion pressure of the tissues, with dilitation and stasis of blood in the capillary bed and loss of intravascular fluid into the extracellular tissue space.[53]

As the individual tissues have varying degrees of sensitivity to vasoactive substances and nervous impulses, it is possible for marked vasoconstriction in one vascular bed (such as the skin) to compensate for capillary pooling in another vascular bed (such as the viscera) and it would be possible to demonstrate little, if any change in peripheral resistance, as usually measured. The final effect of slowing of circulation time and decrease in venous return, however, would be severely detrimental to the organism as a whole.
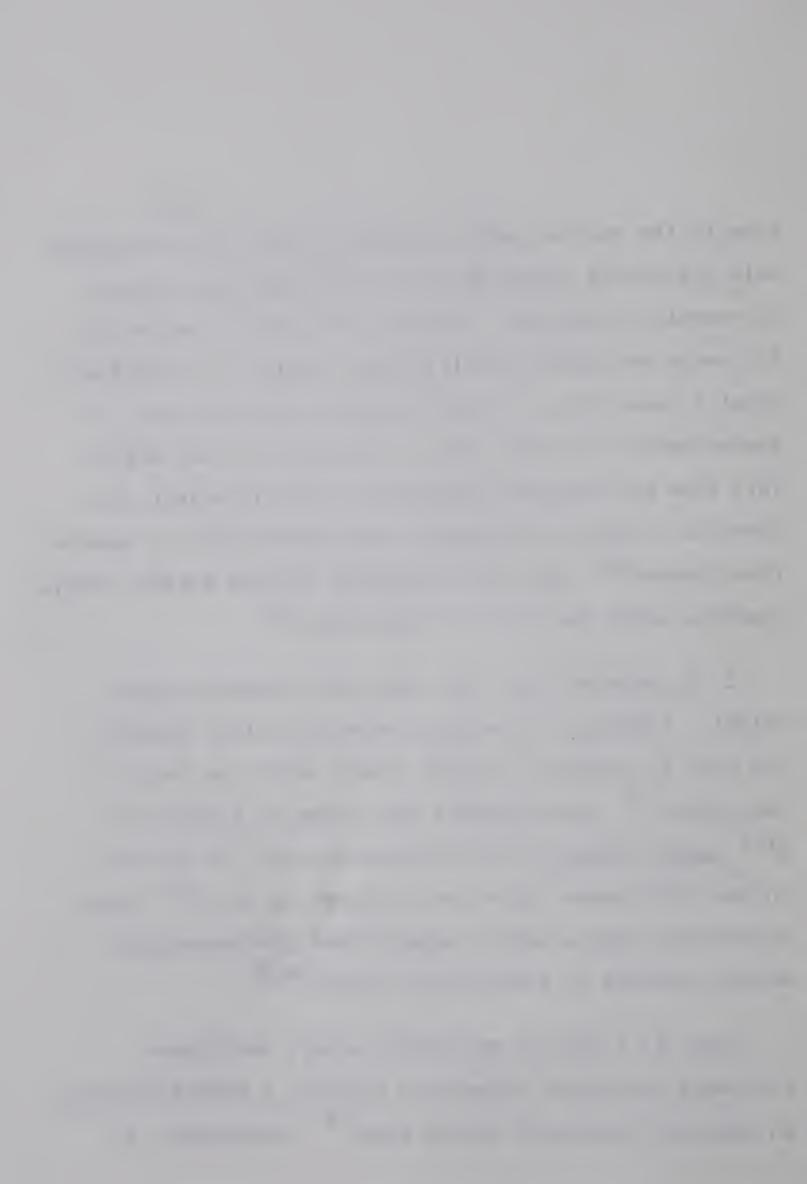
The consequence of these changes can be demonstrated in the liver of the dog. It is reported that there are increased amounts of smooth muscle in the walls of the main hepatic veins which are sensitive to vasoactive substances.[33,34] Others feel that there is smooth muscle

even in the smaller post-sinusoidal vessels in the hepatic vein collecting system which is responsible for changes in vascular resistance. Whatever the precise mechanism, following endotoxin administration, there is an immediate hepatic congestion, a rise in portal venous pressure to approximately 15 mm Hg. and an increase in liver weight. This rise in the portal pressure is only transient, for there is a return to a normal level within five to twenty-five minutes.[33] The liver continues to gain weight slowly, however, until the death of the animal.[34]

It is observed also that the small intestine gains weight. Initially the weight increases rather quickly, and then it continues to gain slowly until the death of the animal.[34] Investigators have shown an increase in I^{131} tagged albumin in the intestinal wall, an increase in the thiocyanate space and no change in the Cr^{51} tagged erythrocyte space, which suggests that the increasing weight consists of interstitial fluid.[54,55]

There is a rise in mesenteric artery resistance following endotoxin; flowmeters indicate a marked decrease in superior mesenteric artery flow.[19] Furthermore, it

has been suggested, both by D_2O studies in an isolated
segment of intestine and by pathological studies of
tissue samples, that capillary flow to the mucosa is
markedly decreased, which suggests the opening of arterio-
venous shunts.[54] The large intestine appears to be
mostly unaffected. The gall bladder becomes quite edem-
atous.[31]

Pulmonary vascular resistance in the intact dog or
in an isolated lung of the dog which has received endo-
toxin, becomes increased. In the isolated lung pre-
paration perfused with homologous blood and endotoxin, a
rise in pulmonary arterial pressure and in pulmonary
wedge pressure is produced. Lung weight shows an average
gain of 8 percent. Pressure studies with small catheters
show that pulmonary venous resistance increases to a
greater extent than pulmonary arterial pressure. These
changes are of rapid onset and largely disappear within
thirty minutes.[56]

Quite a different result is manifested in the kidney;
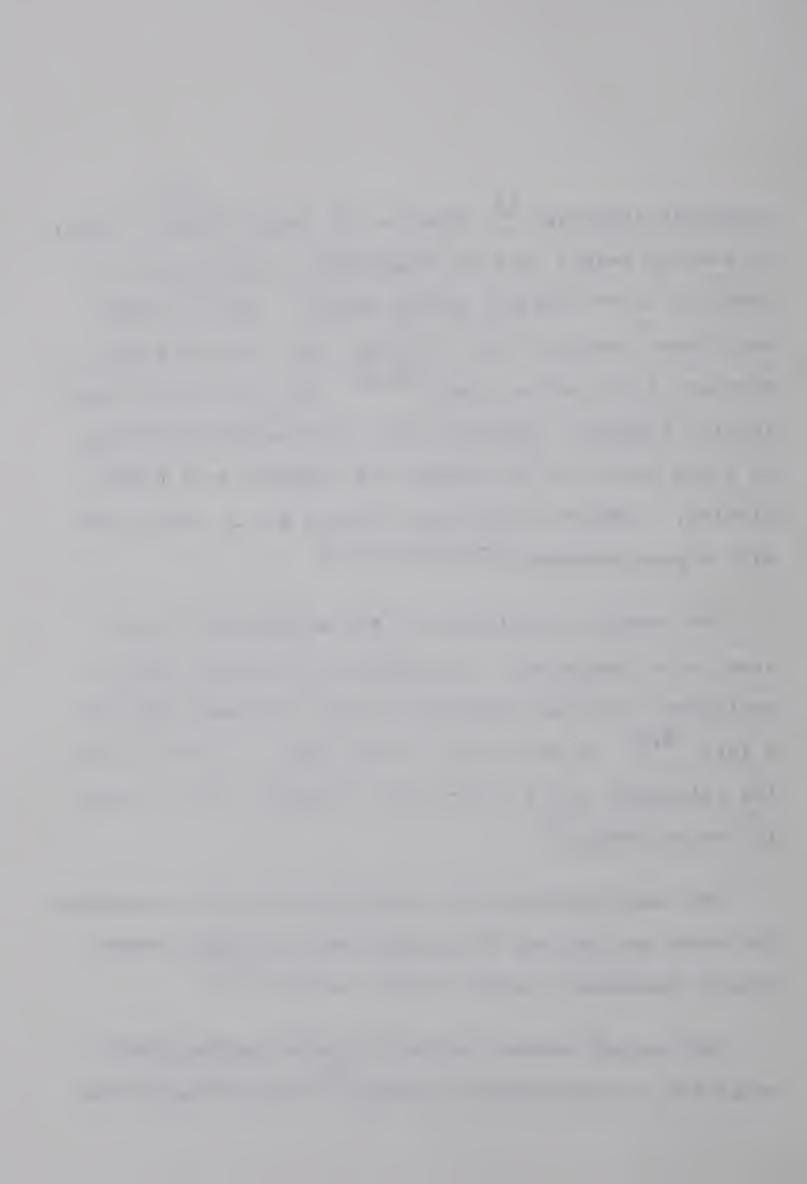a gradual weight decrease begins immediately following

endotoxin injection.[58] From ten to twenty minutes later,
an average weight loss of 25 percent is discovered, as
compared to the initial kidney weight. Renal arterial
resistance usually rises at first, but, after fifteen
minutes, falls below normal.[58,59] This, and other exper-
imental evidence, suggests that arteriovenous shunting
of blood occurs in the kidney and oliguria is a common
finding. Complete anuria may develop and is associated
with a poor prognosis.[59,60,71,72,74]

The vascular reactions for the extremities do not
seem to be consistent. In general, an initial rise in
peripheral vascular resistance occurs followed later by
a fall.[38,43] In most cases, weight gain is detected in
the extremity, but in some cases a weight loss is noted
in the extremity.[73]

The heart maintains its ability to function throughout
the shock period, and if provided with adequate venous
return, produces a normal cardiac output.[33,75]

The central nervous system is spared during shock,
until the very preterminal period.[30] Blood flow in the

REDRAWN FROM: LILLEHEI, R C LONGERBEAM, J. K.
and ROSENBERG,
(Reference 19.)

FIGURE 2

major arteries has been measured in dogs during shock
(Figure 2).[19] There is an initial decrease in the
superior mesenteric artery flow with this low level
continuing throughout the period of shock.[76]

In the renal artery an initial decrease in the flow
is followed shortly by a partial recovery toward normal.
A secondary decrease gradually occurs however, which
then persists until death.[19,77]

As has been mentioned, there is an initial decrease
in the carotid artery flow, but a good recovery occurs.[19,78]
The blood flow then remains stable throughout the hypo-
tensive period until just prior to death. At this time,
there is a secondary severe drop in flow volume, sometimes
amounting to complete cessation of flow.[19,78]

Little drop in flow is recorded in the vertebral
artery. The flow usually returns to normal and remains
thus until the final agonal period, at which time flow
may diminish rapidly.[19]

Total peripheral resistance in eviscerated dogs given
endotoxin progressively falls over a period of one hour.[38]

In spite of some disagreement in the literature, most
authorities agree that some plasma volume is lost from
the "central" circulation, certainly in the latter stages
of shock, and possibly even in the earlier stages as
well.[78] It is interesting to note that the blood volume
and the plasma volume remain fairly normal as measured
by Cr^{51} and I^{131} plasma dilution, which indicates that
the pooling, accounting for the diminished venous return,
is intravascular.[80,81,90]

An initial rise in blood sugar has been well docu-
mented and the levels of sugar in the blood remain normal
or elevated during much of the shock period.[82,84] In
the late stages of shock, hypoglycemia has sometimes been
recorded but this is not a consistent finding.[82,84]

There is a marked disturbance of pyruvate metabolism
and an increase in pyruvate in the blood.[40,84] There is
a similar increase in lactic acid concentration in the
blood, which indicates an abnormal and inefficient glucose
utilization.[40,63,83,84] Glycogen stores are markedly
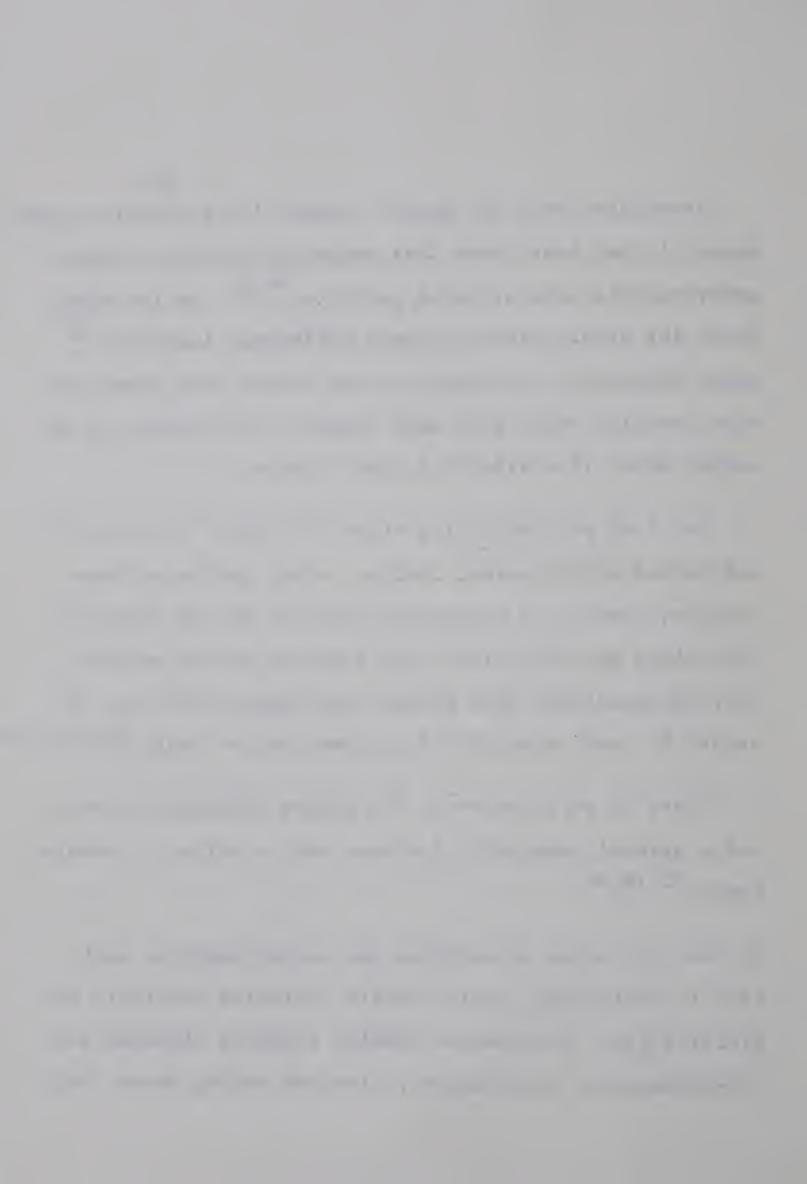depleted.[82]

Associated with the marked changes in circulation noted above, it has been found that oxygen utilization becomes progressively less as shock persists.[85,86] On the other hand, the arterio-venous oxygen difference increases,[85] which indicates a circulation time slower than normal in most vascular beds, with more complete utilization of the oxygen which is available to the tissues.

For long periods during shock, the pH of the blood is maintained within normal limits. After prolonged hypotension, however, a progressive drop in the pH occurs.[63] The animal may die before this drop has become marked; but, on occasions, both animals and humans have been observed to reach a pH of 6.9 or lower before death.[84,85,87,88]

There is an increase in the plasma hemoglobin levels and a gradual hematocrit increase over a period of several hours.[35,78,89]

In the dog, serum epinephrine and nor-epinephrine both rise to quite high levels shortly following endotoxin administration. Epinephrine remains slightly elevated and nor-epinephrine significantly elevated during shock; both
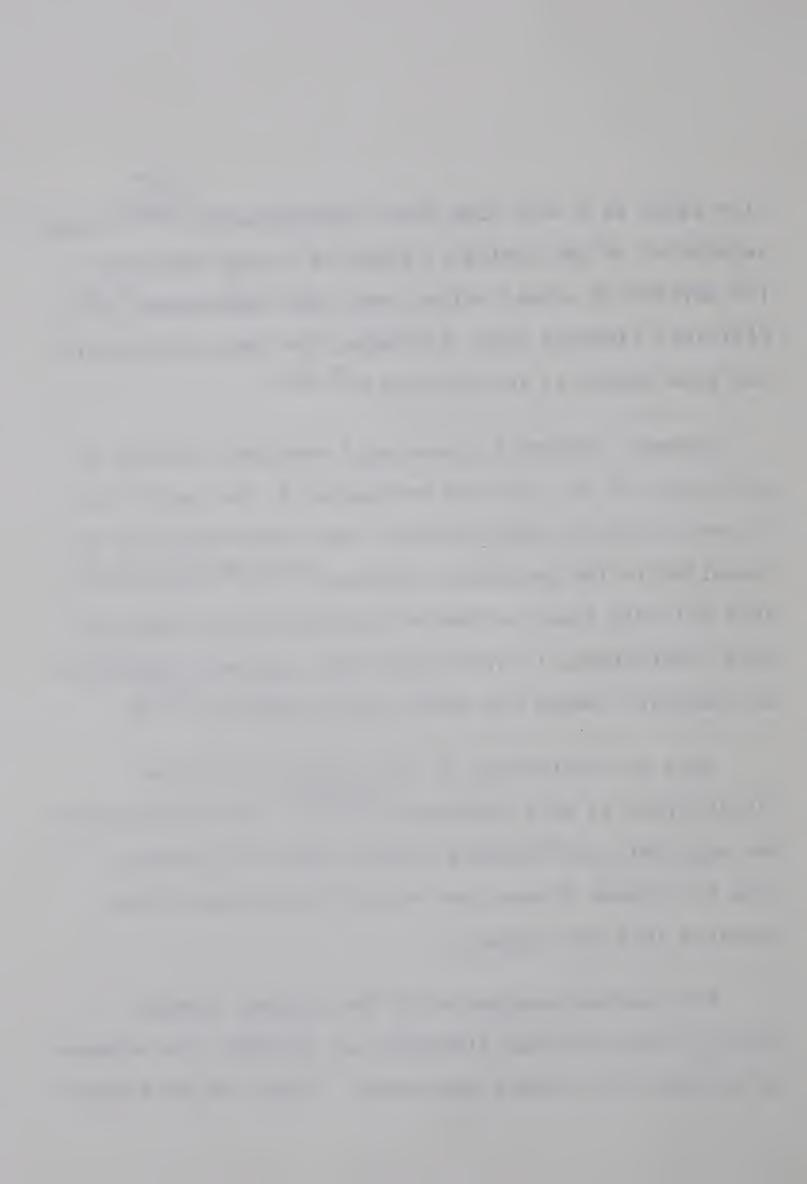
rise again to a very high level preterminally.[39,89] Serum
serotonin, on the contrary, drops to a very low level
(25 percent of normal values) and stays depressed.[39,89]
Platelets likewise drop, following the toxin, but not to
the same degree as the serotonin.[39,89]

Animals exposed to parenteral endotoxin develop an
activation of the clotting mechanisms to the point where
intravascular microembolae have been demonstrated to be
deposited in the peripheral tissues.[63,91,92,93,94,96,97]
This not only slows peripheral circulation and makes it
more inefficient, it also alters the available quantities
of substrate needed for normal clot formation.[95,98]

With the activation of the clotting mechanism,
fibrinolysis is also activated.[92,95,98] The fibrinolysis
can aggravate any bleeding tendency which is present
(due to injured tissues and vessels) and allow diffuse
bleeding into the tissues.

Post-mortem examination of the tissues reveals
several characteristic findings, all of which are evidence
of abnormal circulatory phenomenon. There are no lesions

to suggest any direct action of the endotoxin on tissues. These findings are summarized in the following chart:

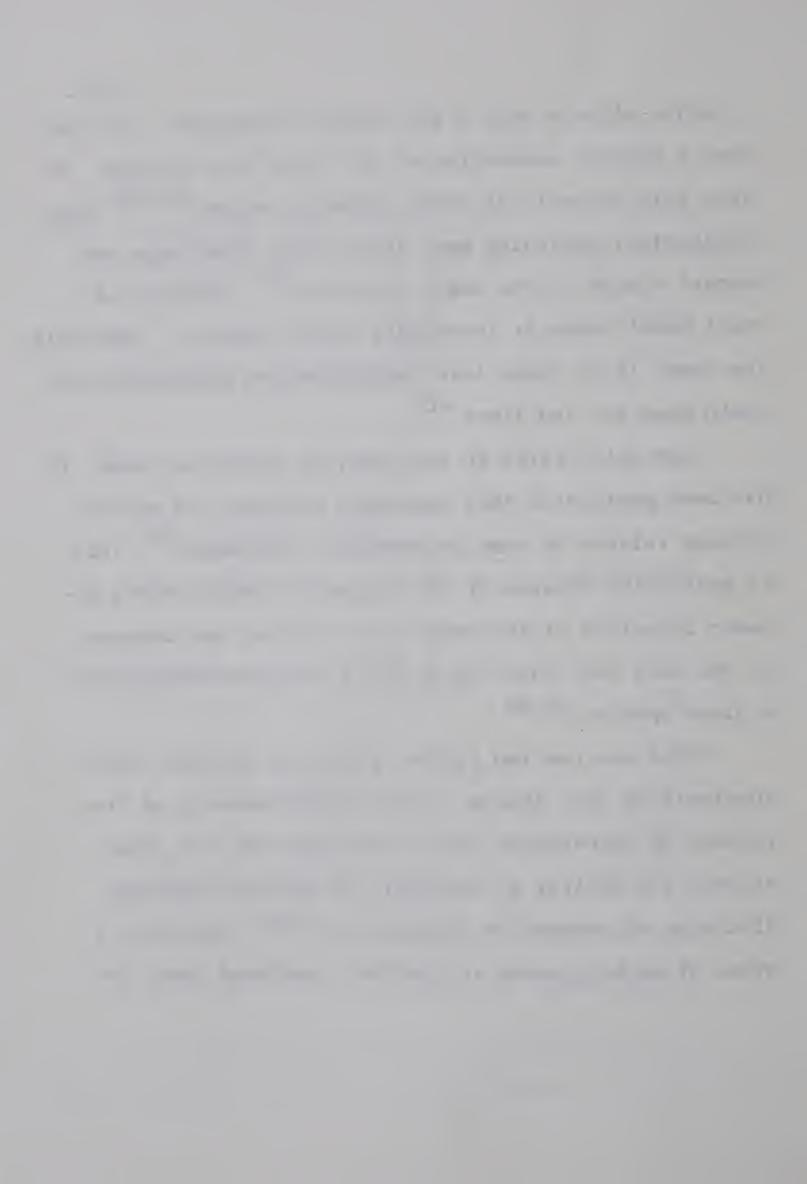|		
BRAIN	-	Normal
HEART	-	Subendocardial hemorrhages, systolic arrest
LUNGS	-	Congestion
ESOPHAGUS	-	Mucosal slough
STOMACH	-	Petechial hemorrhage with or without bleeding
DUODENUM	-	Congestion and hemorrhage
JEJUNUM + ILEUM	-	Mucosal slough, hemorrhage, edema
COLON	-	Edema, petechial hemorrhage
LIVER	-	Congestion, periportal cell death
KIDNEYS	-	Pale, contracted
SPLEEN	-	Small, contracted
BLADDER	-	Edema, petechial hemorrhage present
GALL BLADDER	-	Edema, hemorrhage
MUSCLE GROUPS	-	Pale 12,31,99,100,101

These pathological changes are seen, at autopsy, in dogs dying from endotoxin shock. Other vertebrates show

a similar picture with a few notable exceptions. The cat

shows a greater congestion of the lungs than the dog. At

times this presents as acute pulmonary edema.[50,102] Most

vertebrates, including man, show little hemorrhage and

mucosal slough in the small intestine.[51] Evidence of

small bowel edema is invariably found, however. Generally,

the human liver shows less congestion and periportal cell

death than the dog liver.[60]

From quite early in the study of endotoxic shock, it

has been postulated that endotoxin produces its effects

through release of some intermediary substance.[36] This

is postulated because of the lag period which exists be-

tween injection of the toxin and reaction; and because

of the fact that this lag period is characteristic for

a given species.[51,56]

There are now two further pieces of evidence that

substantiate this theory. First, the discovery of the

release of epinephrine and nor-epinephrine, has demon-

strated the ability of endotoxin to provoke a massive

discharge of vasoactive substances.[19,103] Secondly, a

group of workers using an isolated perfused lung, de-

monstrated that endotoxin produced no effect when profused
with dextran, gelatin solution or plasma. However, it
did produce its characteristic effects on the lung when
perfused with whole blood.[56]

It has been demonstrated by a number of indirect
approaches, that the central nervous system, particularly
the autonomic system, participates in the reaction, to
the detriment of the animal.[30] Sectioning of the sym-
pathetic afferent nerves to the adrenal gland,[104,106,121]
high spinal anaesthesia,[104] barbiturate anaesthesia,[12]
chlorpromazine[19] and its derivatives all have a protective
effect on the shock process; in fact, they may even save
an animal from an otherwise lethal dose of toxin.[19]
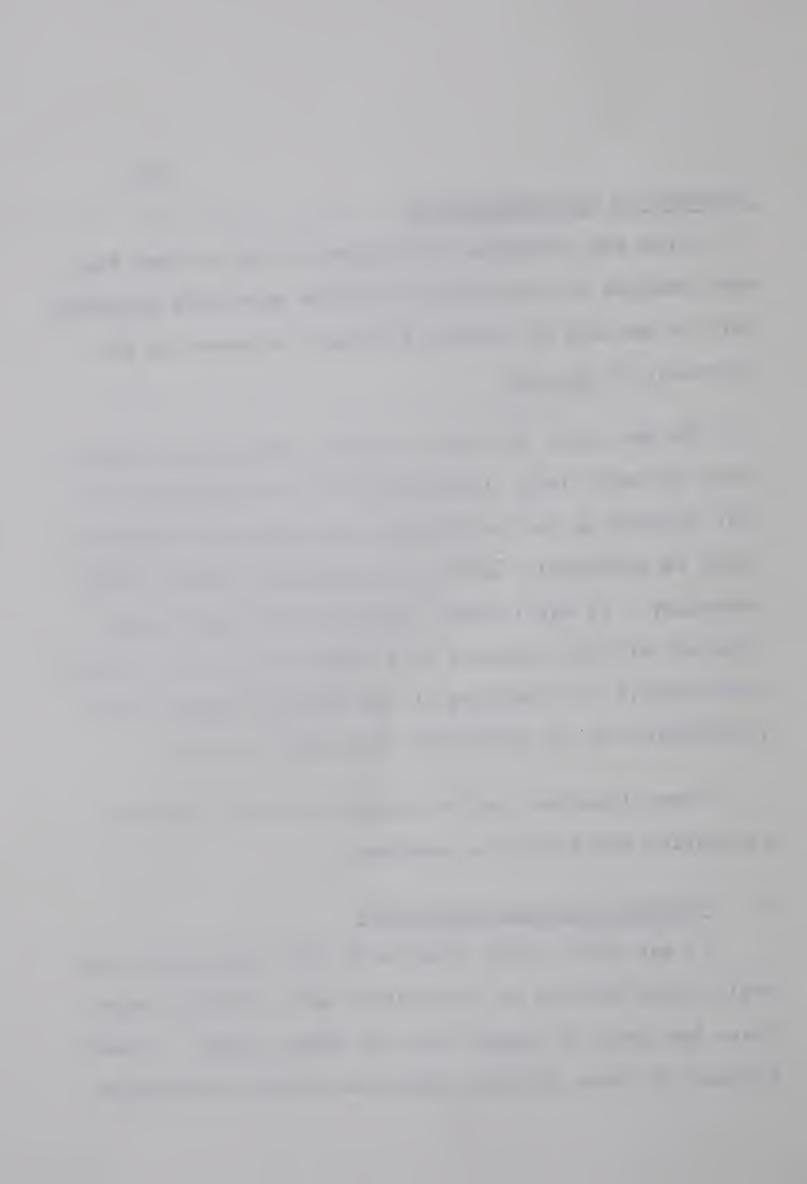
THEORIES OF IRREVERSIBILITY:

From the foregoing discussion it can be seen that
many changes in physiologic function have been recorded,
both in man and in animals following exposure to the
endotoxin of E. coli.

On the basis of their clinical and research exper-
ience in this field, investigators have emphasized cer-
tain aspects of the pathological changes and considered
these as pathogenic, with all subsequent changes being
secondary. It was further suggested that appropriate
reversal of these changes at a sufficiently early period
would result in a halting of the disease process and a
restoration of the individual to normal health.

These theories can be divided into four general
categories which will be examined.

1.   Abnormal Vascular Reactivity

It was first noted clinically that hypotension and
death could develop in association with infection when
there had been no obvious loss of blood volume. Invest-
igation of these shocked individuals with dye dilution

techniques showed the blood volume to be normal or even
increased. Adding to the circulating volume did not
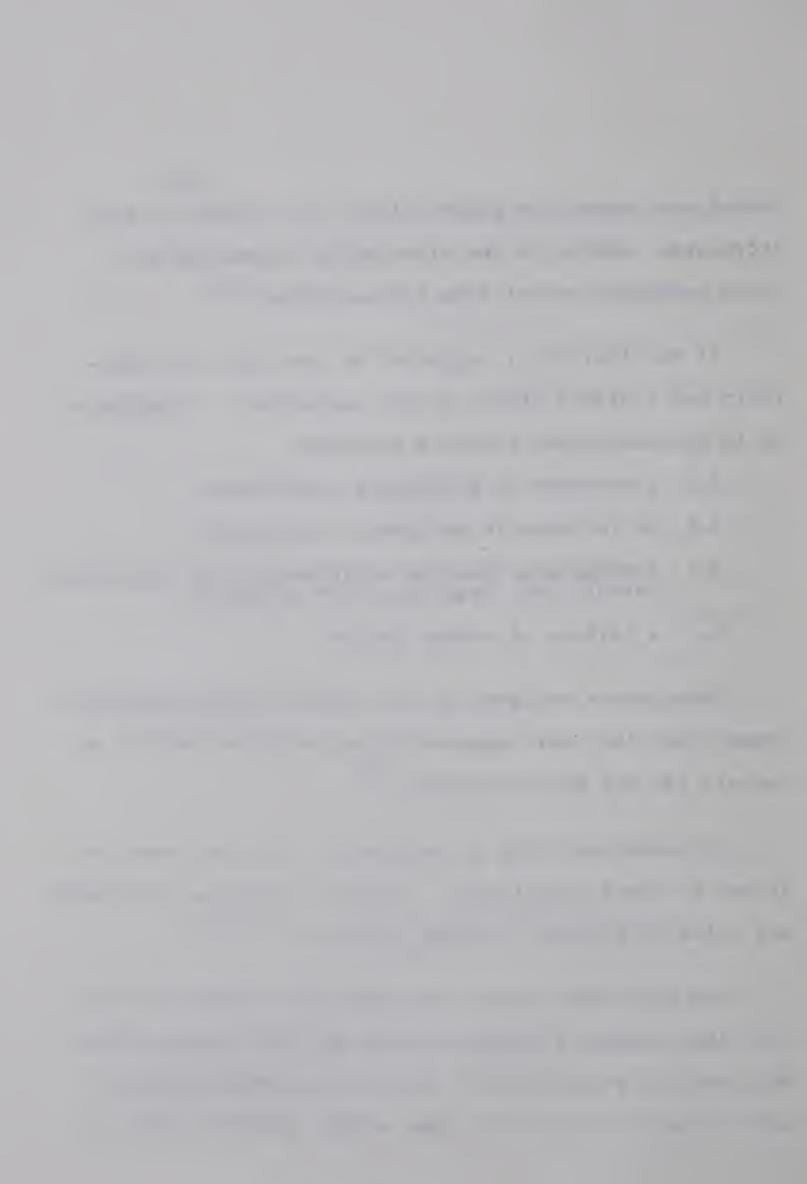bring permanent relief from the condition.[105]

It was therefore, suggested by some that the endo-
toxin had a direct effect on the vasculature. Hypotheses
as to the mechanisms involved included:

   1.) a decrease in peripheral resistance;

   2.) an increase in peripheral resistance;

   3.) a peripheral pooling by dilatation of capacitance
        vessels and "sequestration" of blood;

   4.) a failure of venous return

Experiments designed to test these various hypotheses
showed that the toxin apparently had no direct effect on
vessels (as has been mentioned).[56]

No consistent drop in peripheral resistance was ob-
served in these experiments. Indeed, peripheral resistance
was noted to increase in many instances.[31,32,33]

The fact that venous return was diminished and there-
fore that cardiac filling was poor was well documented by
Weil and his associates.[33] It was also demonstrated in
many tissues in dogs that organ weight progressively in-

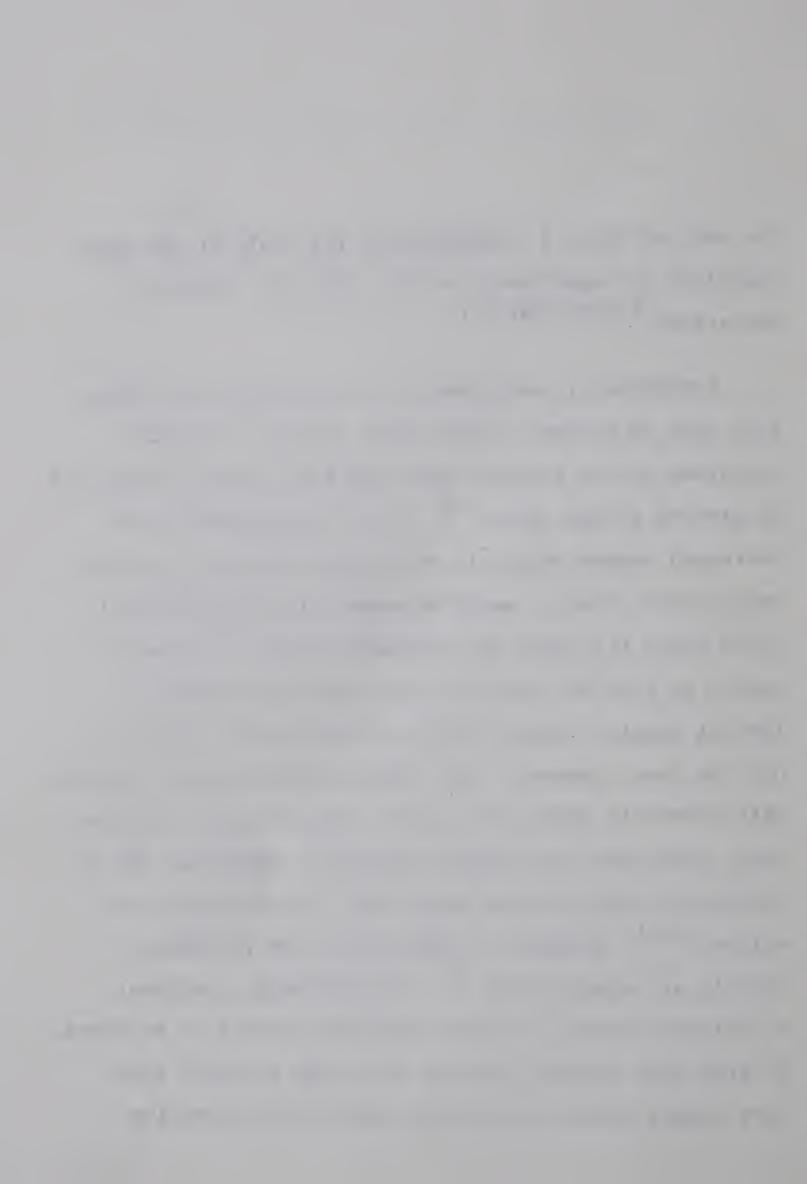creased and the organs became congested, edematous and
even hemorrhagic.[34]

The mechanism by which this venous return was de-
pressed was less perfectly understood. Some suggested
that it was a passive process secondary to a decreased
flow rate (or perfusion pressure).[33] Others hypothesized
a decreased tissue pressure or loss of capillary "tone"
through anoxia or a primary loss of venous tone.[60]
Others observed a spasm of the post-capillary capacitance
vessels which was maintained during shock.[107,108]

With the following facts taken into consideration
it can be seen that the peripheral pooling of blood is
not a passive process. Careful studies of capillary beds
have failed to reveal any neural or humoral mechanism by
which the capillaries can alter their own volume (with
the possible exception of swelling of the endothelial
cells).[109] There is insufficient smooth muscle around
their walls to effectively contract or dilate. Instead,
it has been demonstrated that the introduction of blood
to the capillary bed is controlled by the state of con-
traction or relaxation of the precapillary sphincter.

The exit of blood is regulated by the state of the post-
capillary or capacitance vessels and their sphincter
mechanisms.[60,107,108,109]

Furthermore, measurements in normal man have shown
that only 30 percent of the blood volume is normally
contained in the arteries and capillaries while 70 percent
is present in the veins.[110] If it is postulated that
decreased venous return is occurring because of lack of
venous tone, then it would be expected that peripheral
veins would fill with the increased volume. One would
expect to find the central venous pressure normal or
low but jugular venous filling to be present. This is
not the case, however. The typical picture of the patient
with endotoxic shock of a severe degree is of a confused,
cool, ashen-grey (or mottled cyanotic) individual who is
frequently noted to have moist skin (an adrenergic re-
action).[3,51] Attempts to take blood from peripheral
vessels are unsuccessful.[70] In performing a cutdown,
a collapsed vessel is found containing little or no blood.
A large bore cannula inserted into such a vessel runs
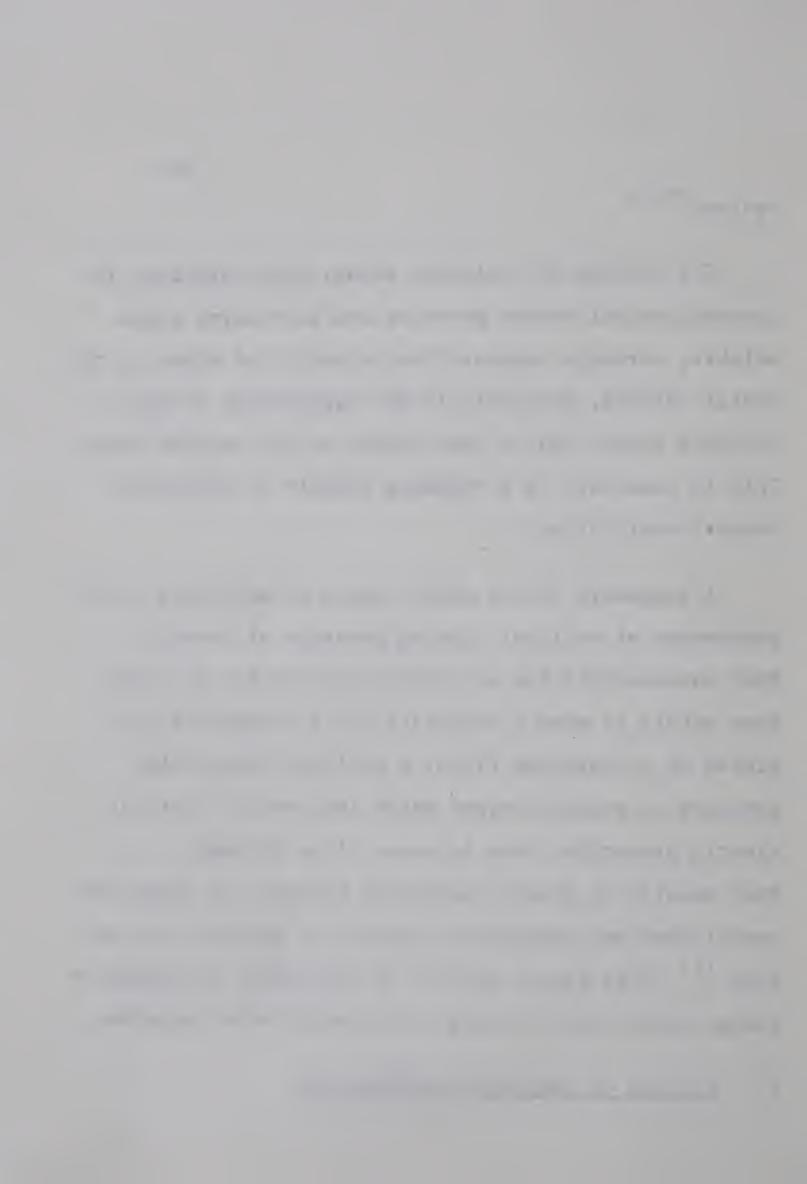very slowly unless pressure is added to the infusion

system.[70,73]

The finding of collapsed veins, pale coloring, de-
creased central venous pressure and increasing organ
weights, strongly suggests the retention of blood in the
distal vessels, primarily in the capillaries of dis-
tensible organs and to some degree in the smaller veins.
This is secondary to a "damming effect" of increased
venous constriction.

A secondary effect which should be mentioned is the
phenomenon of critical closing pressure of vessels.
When vasoconstriction of either the arterial or venous
tree occurs or when a capillary bed is temporarily de-
pleted of circulating fluid, a critical hydrostatic
pressure is reached beyond which the vessel's natural
elastic properties tend to cause it to collapse. It
then requires a greater perfusion pressure to reopen the
vessel than was originally required to maintain its pat-
ency.[111] This factor must be an additional non-adaptive
change which occurs during severe hypotensive episodes.

2.   Failure of Specific Organ Systems

A.   Primary Cardiac Failure: In the early con-
sideration of shock associated with infection there was
much speculation that the heart was affected by toxic
products and was responsible for the subsequent deleter-
ious circulatory changes.   This idea was substantiated
further when it was shown that peripheral resistance
remained stable while cardiac output was found to be
decreased.[32,86]

It was soon shown, however that in these conditions
the heart could respond with increased output when supplied
with a greater venous return.   Also, no consistent ECG
change or arrhythmia was observed during shock caused by
endotoxins.[57,113]

Subsequent investigations have strongly suggested
that, though the decreased myocardial function is not the
primary cause of hypotension, there comes a time when the
heart muscle itself begins to fail.[86,114]   In other types
of prolonged hypotension, it has been shown that life can
be prolonged and mortality reduced by digitalization.[112]

There remains some controversy as to whether this

terminal cardiac decompensation is a toxic effect on the myocardium caused by endotoxin, or whether it is secondary to the hypoxia which develops during hypotension.[115] Recent studies by Guyton have shown cardiac decompensation to be directly related to the degree of hypoxia which an animal sustains.[112] This suggests that hypoxia and the related acidosis is responsible for cardiac failure rather than specific toxic factors.[112,115]
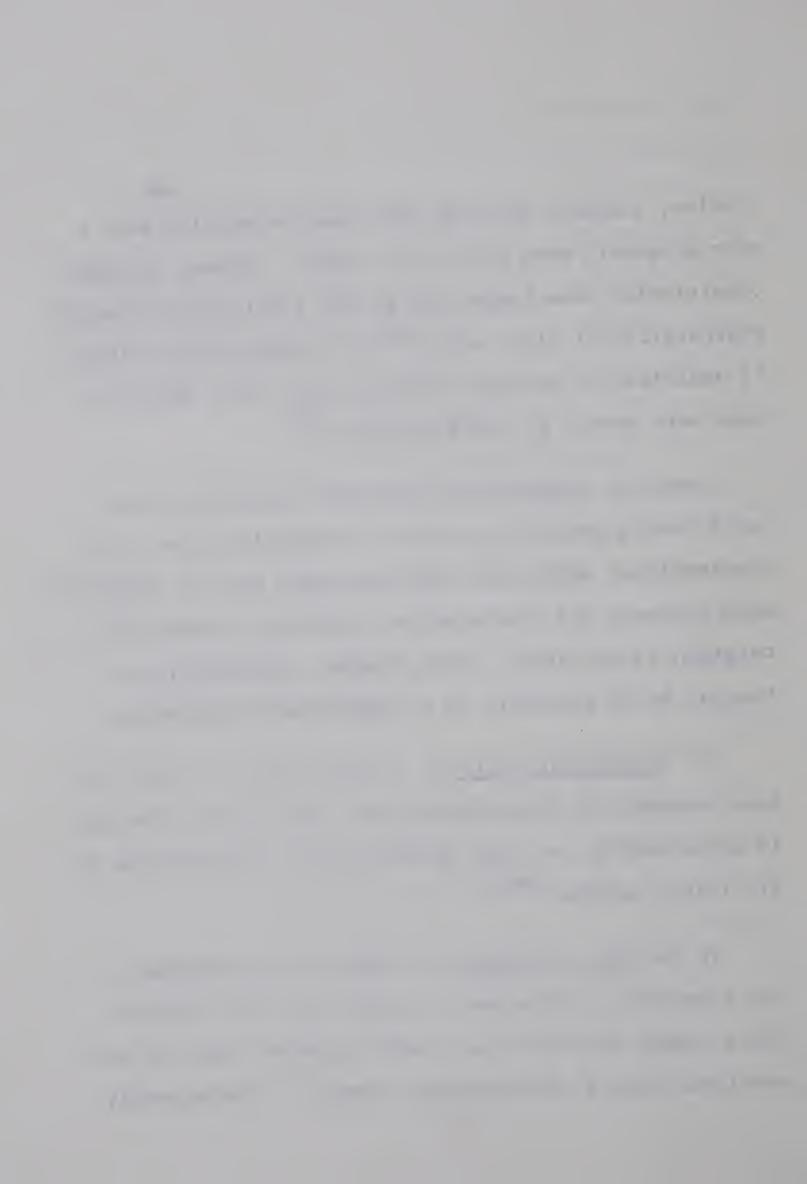
B. <u>Renal Failure</u>: In man and in animals early oliguria and anuria is consistently seen during shock in association with endotoxins. The degree of urinary output and its response to treatment is a fairly reliable prognostic sign as to the eventual outcome of the patient. Though urinary failure aggravates the shock state by failing to excrete toxic products and by failing to perform its buffering function, there are many cases in which recovery from shock was accomplished while the patient remained anuric.[40] This strongly implies that kidney failure is not the lethal mechanism through which endotoxin works.

C. <u>Hepatic Failure</u>: In man, abnormal liver function

studies, jaundice and coma have been associated with a poor prognosis when present in shock. Autopsy findings consistently show congestion of the liver with periportal degeneration of liver cells.[51] In animal studies there is depletion of glycogen stores in the liver which become more severe as shock persists.[116]

However, abnormalities of liver function are not consistently present in clinical endotoxin shock. The abnormalities which have been described are all compatible with recovery and regeneration, provided a normal circulation is restored. These changes, therefore, are thought to be secondary to a compromised circulation.

D. Intestinal Failure: A great deal of effort has been expended in investigating the role of the intestine in perpetuating the shock process and in contributing to its lethal outcome.[36,37]
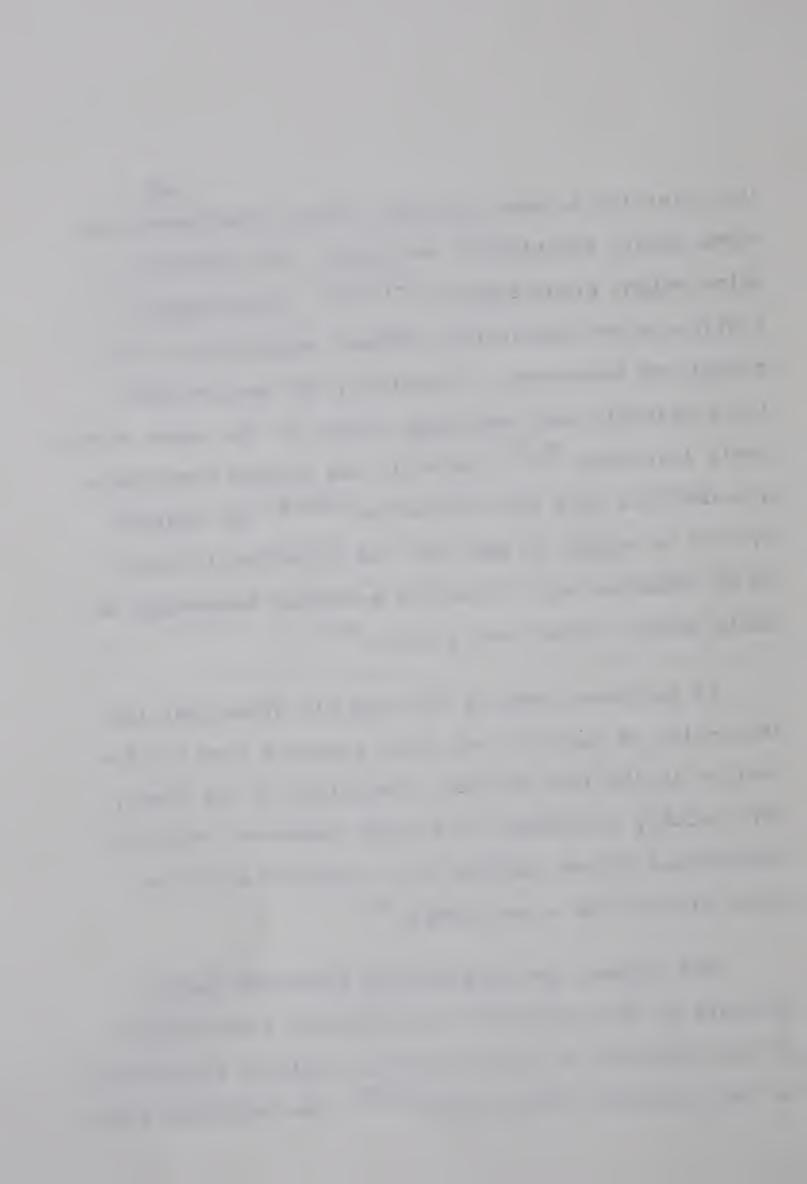
In the dog, following an injection of endotoxin, the intestine is observed to blanch, and its arterial blood supply decreases to a degree greater than the proportional drop in the systemic supply.[19] Subsequently

the intestine becomes cyanotic; venous engorgement and
edema occur; peristalsis decreases. The intestine
gains weight progressively.[34,55,117] Histological
sections show degenerative changes occurring in the
mucosa and sub-mucosa. Eventually the mucosa loses
its continuity and hemorrhage occurs in the lumen of the
small intestine.[35,92] Bacteria and altered hemoglobin
are absorbed into the circulation.[35,68] The changes
are not as marked in man, but the intestine is found
to be edematous and frequently petechial hemorrhage or
small mucosal ulcers are present.[51]

It has been shown by Fine and his group that the
absorption of bacteria and their products from the in-
testine in the face of poor circulation to the liver,
very quickly overwhelms an already depressed reticulo-
endothelial system leading to an aggravation of the
shock process and a bacteremia.[68]

This process can be partially prevented (with a
decrease in the mortality) by antibiotic sterilization
of the intestine or by perferential assisted circulation
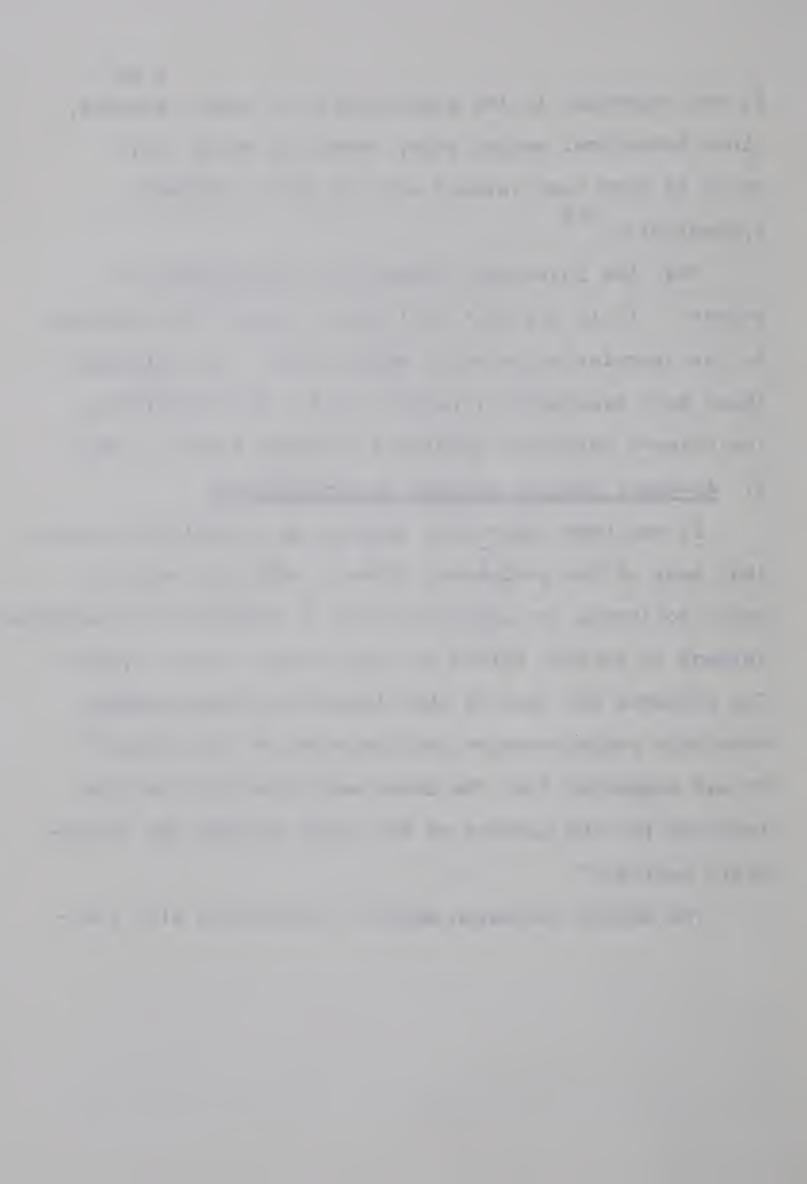to the intestine during shock.[25,37] The bacterial factor

is not essential to the perpetuation of shock, however,
since intestinal weight gain, edema and death still
occur in germ free animals who are given endotoxin
systemically.[118]

That the intestinal changes are deleterious is
evident. It is now felt that these changes are secondary
to the vascular adjustments which occur. The intestine
shows more prominently, because of its distensibility,
the changes which are occurring in other organs as well.

3. Abnormal Central Nervous System Reflexes

It has been suggested, largely on an empirical basis,
that many of the peripheral effects which are noted to
occur following the administration of endotoxin are mediated
through an initial effect on the central nervous system.
The evidence for this is that there is a delay between
endotoxin administration and the onset of its action.[51]
It was suggested that the delay was caused by the time
required for the passage of the toxin through the "blood-
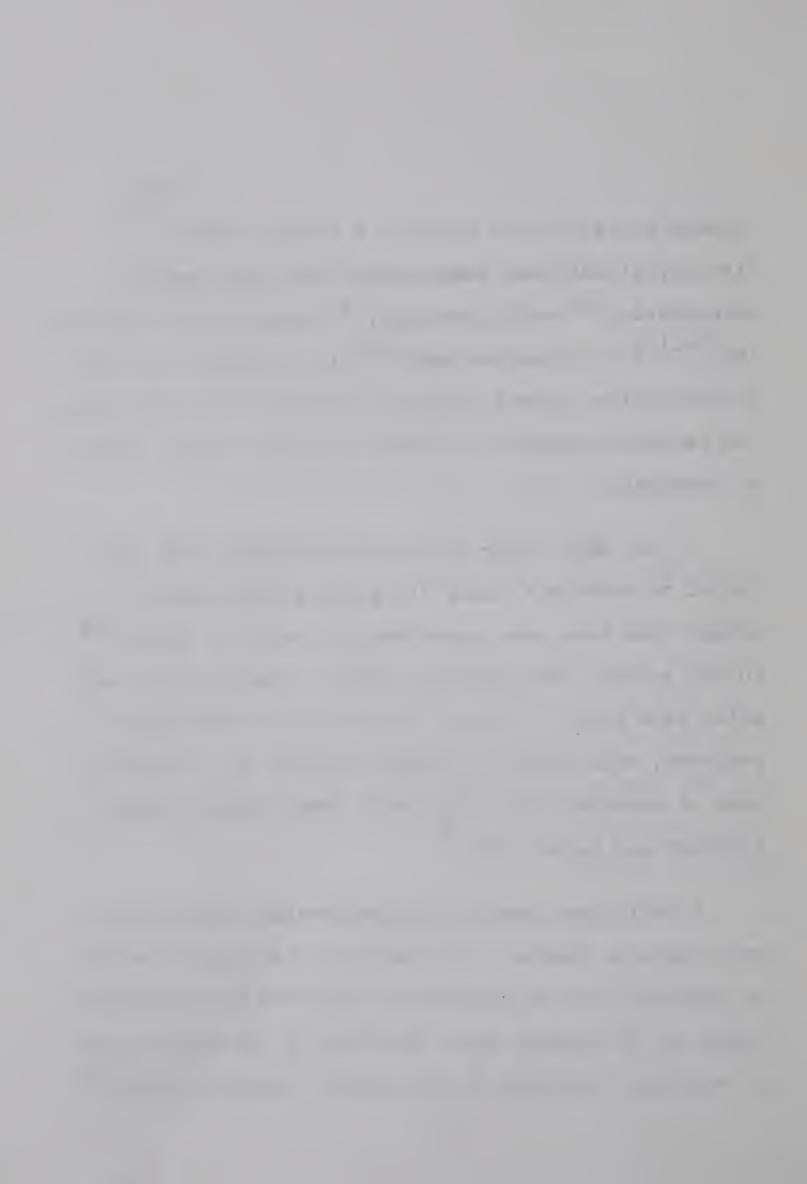brain barrier."

The mental confusion which is associated with endo-

toxemia has also been noted as a central effect.[51]
Finally, it has been demonstrated that high spinal
anaesthesia,[104] chlorpromazine,[19] adrenal nerve section-
ing[104,121] or sympathectomy,[106] all of which, directly
or indirectly, affect nervous adjustment of circulation,
can partially protect an animal from the lethal effects
of endotoxin.

It has been noted that unanaesthetized dogs sub-
jected to endotoxic shock die earlier than similar
animals who have been anaesthetized prior to shock.[119]
In one series, dogs having a higher blood pressure and
pulse rate prior to shock (indicating an adrenergic
response) were noted to succumb earlier to a standard
dose of endotoxin than dogs with lower initial blood
pressure and pulse rate.[35]

A sufficient amount of experimental evidence has
been amassed, however, to show that the changes caused
by endotoxin can be produced in isolated and denervated
organs or in animals after division of the spinal cord
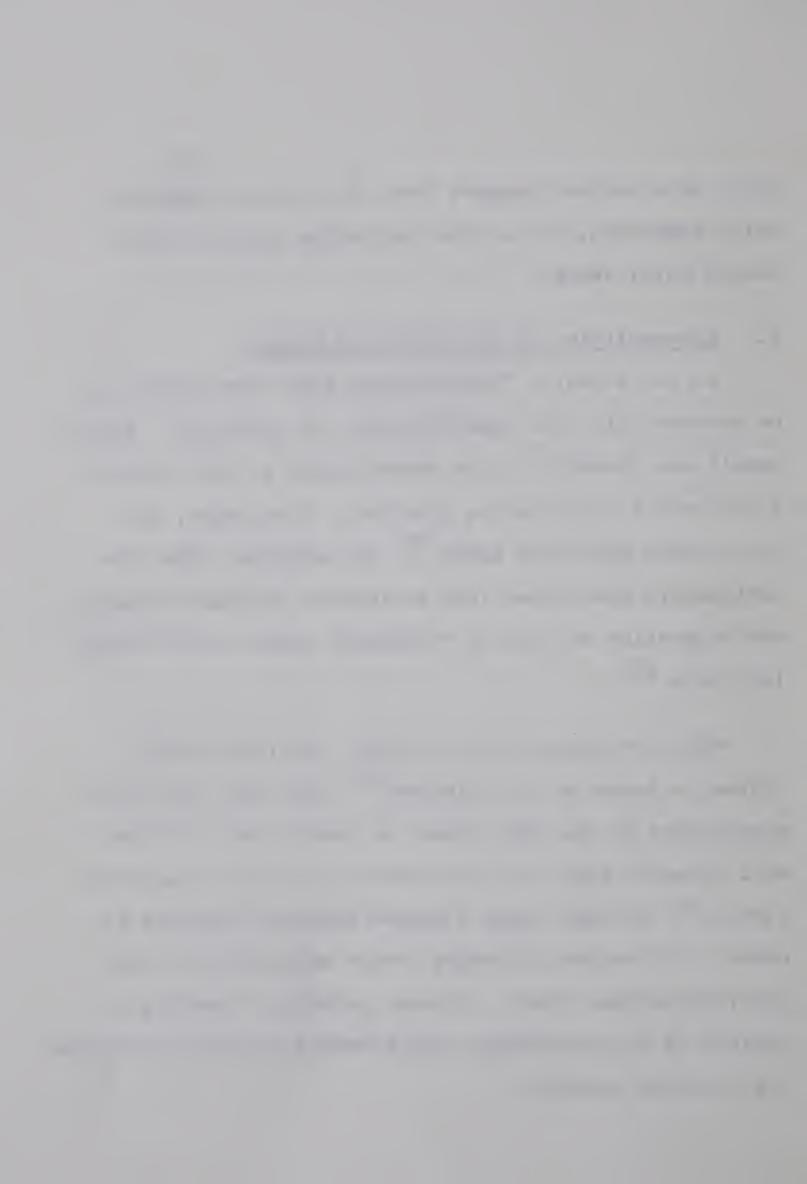or vascular isolation of the central nervous system.[30]

These observations suggest that the central component, while important, is not the initiating factor in producing fatal shock.

4.   Abnormalities of the Blood and Plasma

In the animal a "Schwartzmann-like" phenomenon can be observed with the administration of endotoxin. Microemboli and thrombin can be demonstrated in the tissues; a decrease in circulating platelets, fibrinogen, and prothrombin have been noted.[95] In addition, other investigators have shown that peripheral rouleaux formation and stagnation of flow or "sludging" occurs in the capillary beds.[120]

With the progression of shock, the fibrinolytic system is found to be activated.[95] This can reach such proportions in the late stages of shock that the blood will actually begin to lyse before a clot has completely formed.[95] At this stage a marked bleeding tendency is noted. In the dog, bleeding occurs primarily into the gastrointestinal tract. In man, petechial bleeding is noticed of the extremities and bleeding into the intestinal tract is not unusual.
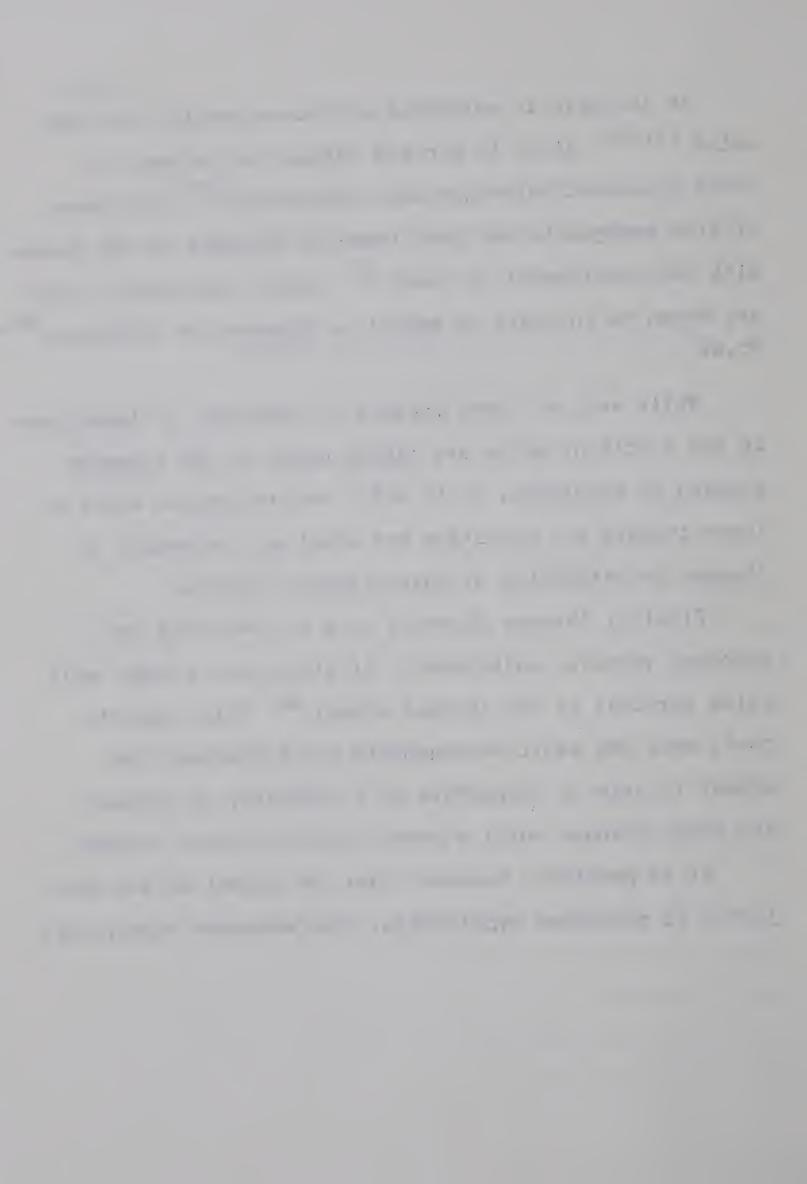
An increase in adrenalin and nor-adrenalin has been noted.[19,121] Also, in man and animals an increase in serum glucocorticoids has been documented.[122] The level of free hemoglobin has been found to increase in the plasma with the development of shock.[35] Lactic and pyruvic acids are known to increase in amount as hypotension continues.[84,85,60]

While each of these factors is doubtless of importance in the reactions which are taking place in the organism exposed to endotoxin, it is still not determined which of these changes are causative and which are secondary to changes in metabolism or physiological function.

Finally, therapy directed only at reversing the abnormal vascular adjustments, if given soon enough, will allow survival of the shocked animal.[60] This suggests that, once the basic derangements are corrected, the animal is able to compensate for, tolerate, or correct the other changes until a normal state has been reached.

It is possible, however, that the animal or man subjected to prolonged hypotension, from whatever cause, will

experience abnormalities of function in all systems
mentioned. Survival of these severely stressed individuals
will then depend on therapy specifically planned to deal
with as many of these abnormalities as is possible. [105]
No simple approach will suffice.

A review of the literature describing cases of endo-
toxin shock in humans revealed that 30 to 50 percent of
all cases would survive with little treatment other than
antibiotics, antipyrexics, fluid and blood replacement
(in other words, with supportive therapy).

In addition, the experimental literature is abundant
with studies which show a decreased mortality with various
types of therapy, provided this therapy were started prior
to the onset of shock, or within a short time after its
inception.

Gans, Krivit and Hardeway demonstrated that the
intravenous administration of endotoxin was associated
with the deposition of microthrombi in the peripheral
vasculature. Subsequently, an increased fibrinolytic
activity in the blood was noted.[91,97] By administration
of heparin in therapeutic doses prior to endotoxin, these
investigators showed that the microthrombi deposition
could be prevented.[91,97] It was demonstrated, however,
that a large dose of endotoxin still caused hypotension
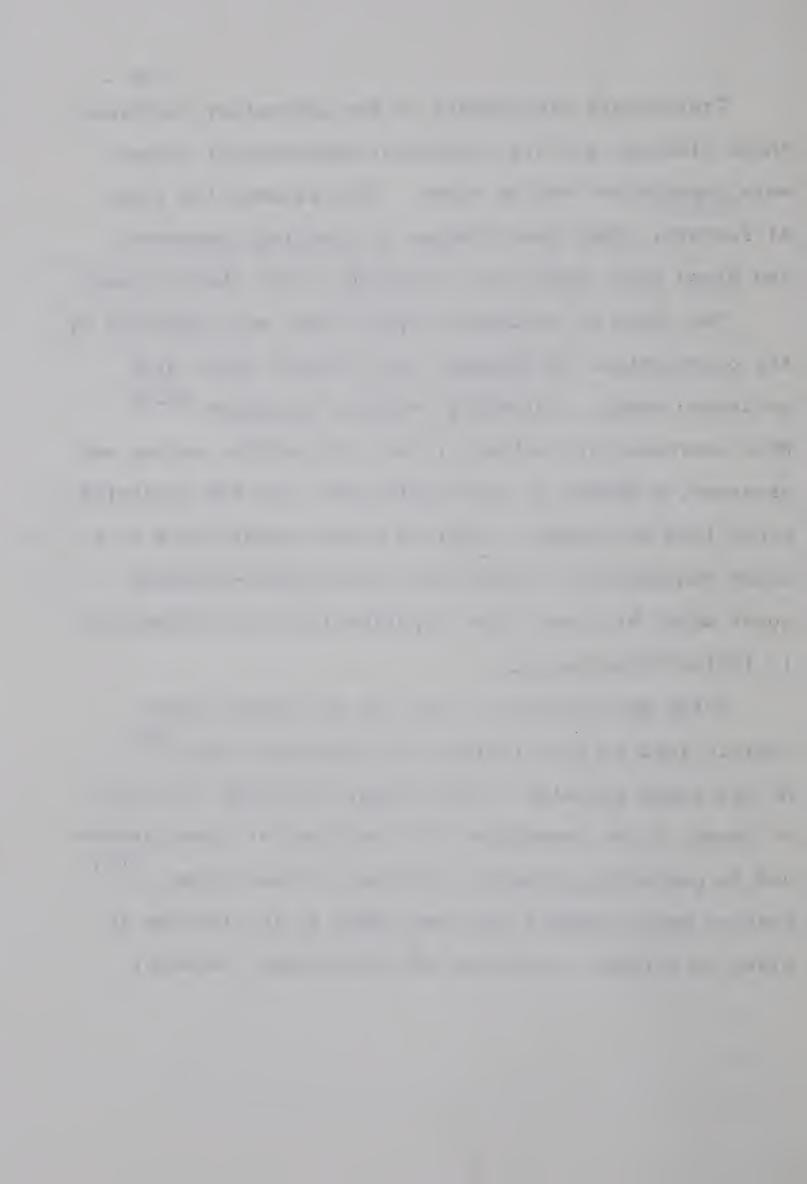and death in the presence of heparinization.[97]

Preliminary experiments in the laboratory confirmed these findings and all subsequent experimental animals were heparinized during shock. This allowed the study of factors, other than changes in clotting components and blood loss, which were involved in the shock process.

The study of euglobulin lysis times was suggested by the observations of Hardeway and Lillohei that, with prolonged shock, a bleeding tendency developed.[36,95] When increased activation of the fibrinolytic system was observed, a method of controlling this and the excessive blood loss was sought. Epsilon amino caproic acid is a known non-specific, competitive proteolytic-blocking agent which has been shown experimentally and clinically to inhibit fibrinolysis.

Spink had reported on the use of epsilon amino caproic acid in the treatment of endotoxin shock.[123] He had found infusion of this drug, following the onset of shock, to be beneficial in reversing the shock process and in producing permanent survival in some animals.[123] Epsilon amino caproic acid was added to the therapy in order to attempt to control the hemorrhagic tendency.

Studies of euglobulin lysis time were carried out both before and after treatment in order to evaluate the effectiveness of this drug.

Several investigative groups have referred to acidotic changes in pH and drops in pCO_2 during endotoxin shock.[85] Little investigation of the significance of these changes, or of the magnitude of the changes in relation to the body's buffer reserve, is recorded. Those groups reporting efforts at therapeutic modification of acidosis have utilized amine buffers. "Tris" and "Tham" have proven to be remarkably ineffective in altering the lethal outcome of the shock process.[88,124]

Clinical reviews devoted to a discussion of the treatment of endotoxin shock suggest that acidosis should be corrected in the severely shocked patient.[83,85] They suggest that sodium bicarbonate should be used but no results are reported to prove its effectiveness.[114] Work, which had previously been performed in this laboratory and in other centers, suggests that a significant tissue acidosis does exist during shock. One of the project's prime purposes was to investigate this possibility.

When methods were devised to measure, indirectly,
the magnitude of this acidosis, the buffering systems
were restored toward a normal range with sodium bicar-
bonate administration. More bicarbonate was given later
in the treatment period if subsequent blood pH and pCO_2
determinations suggested initial inadequate buffering.

Many groups have shown that vasoconstriction and
a drop in perfusion pressure occurs in the systemic
circulation.[19,57] These findings were confirmed and,
in addition, the changes in perfusion pressure of the
femoral marrow cavity were recorded. Many drugs have
been evaluated for their ability to reverse the abnormal
vascular responses occuring during shock.[19,59,63,65,79,87,105] One such drug, phenoxybenzamine, has been evaluated
previously in this laboratory and the results published.[48,125] This drug has proven to be a very effective agent
and evaluation of its effect in combination with other
therapy was carried out.

The administration of phenoxybenzamine to normo-
volemic patients or animals increases their apparent in-
travascular volume by about fifteen percent.[126] It was

felt that this increased volume should be filled by the administration of an extracellular volume replacement fluid. An albumin containing tyrode's solution was chosen for this purpose because this solution had been evaluated and found to be an effective plasma substitute by other workers.[127] This volume expander was also given in further amounts in the treatment period if the clinical state of the animal indicated a lowered blood volume.

This investigation was approached with the basic premise that shock originated by introduction of endotoxin is a potentially reversible process and can be successfully treated up to the point of cardiac arrest, providing a sufficient understanding of many of the physiological derangements and their sequence of occurrence could be understood.

An attempt was made to devise a course of treatment which would effectively reverse these specific changes and would restore the animal to a state of physiological balance and thereby prolong the animal's life. The ultimate objective was permanent survival of animals that had undergone prolonged shock.
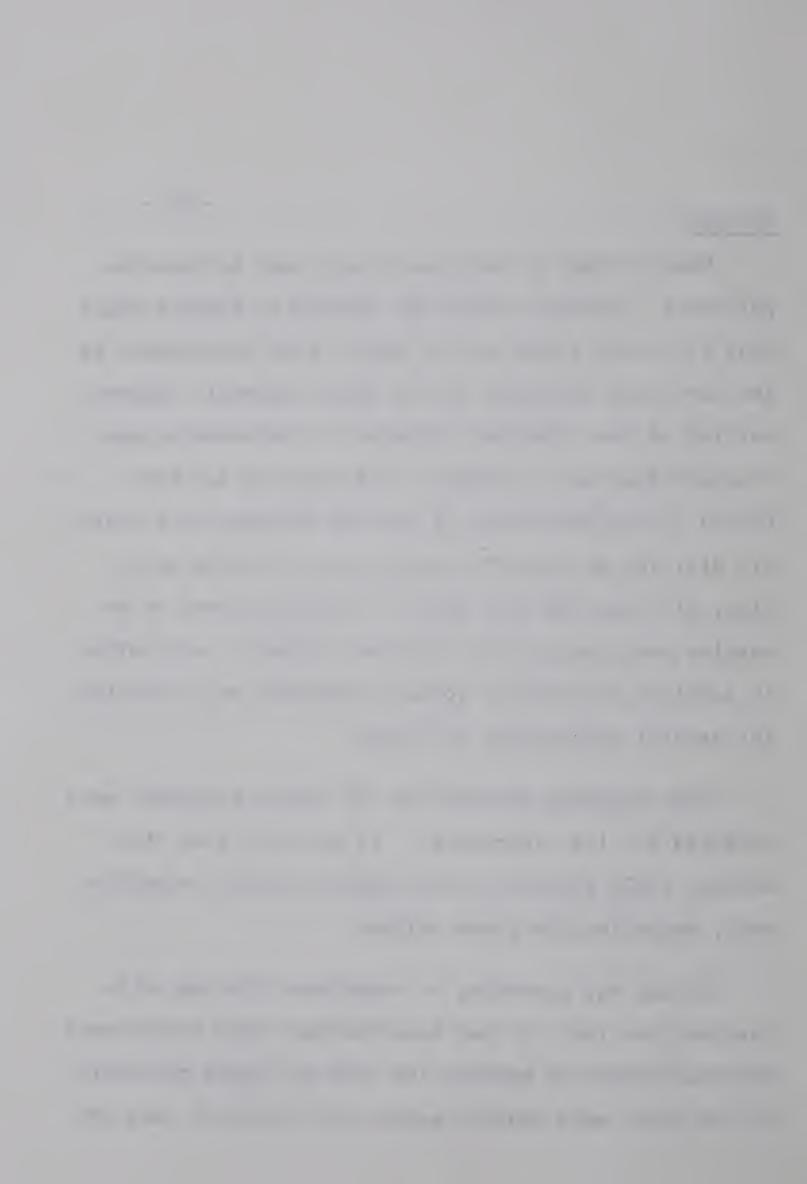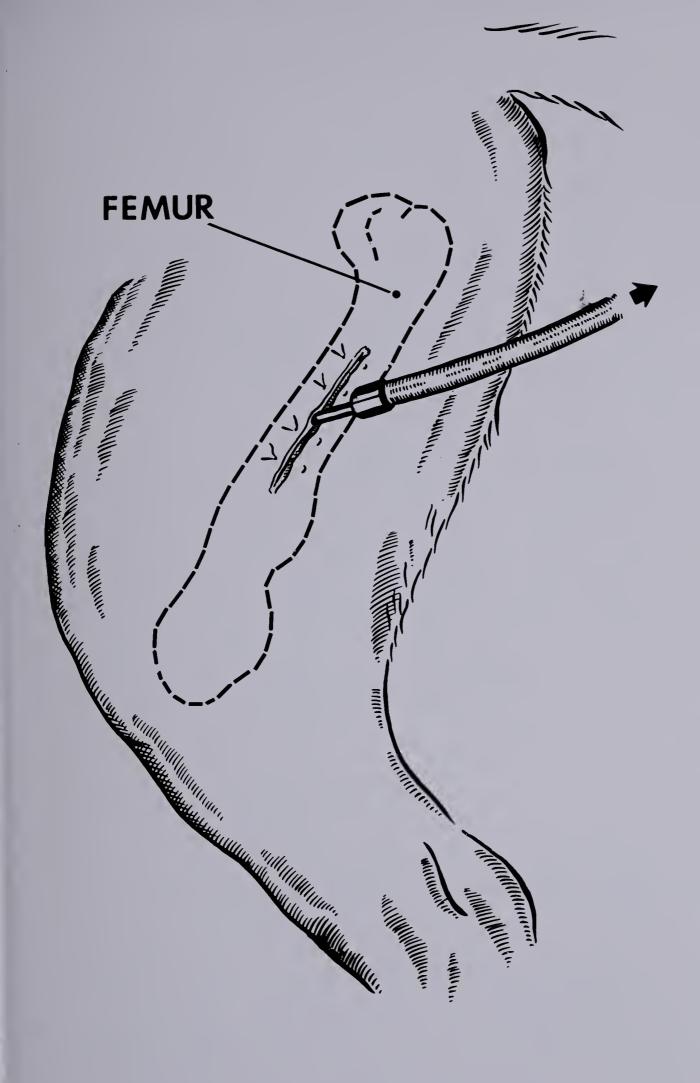
METHODS:

Mongrel dogs of both sexes were used in these ex-
periments. Special effort was exerted to procure adult
dogs (at least a year old or more), with development of
the teeth and condition of the tartar deposits thereon
serving as the principal criteria for determining age.
Pregnant dogs were excluded. The dogs had all been
housed in the University of Alberta vivarium on a stand-
ard diet for at least two weeks prior to being used;
also, all dogs had been given at least one dose of de-
worming medicine and had received distemper vaccination
in addition to whatever special treatment was indicated
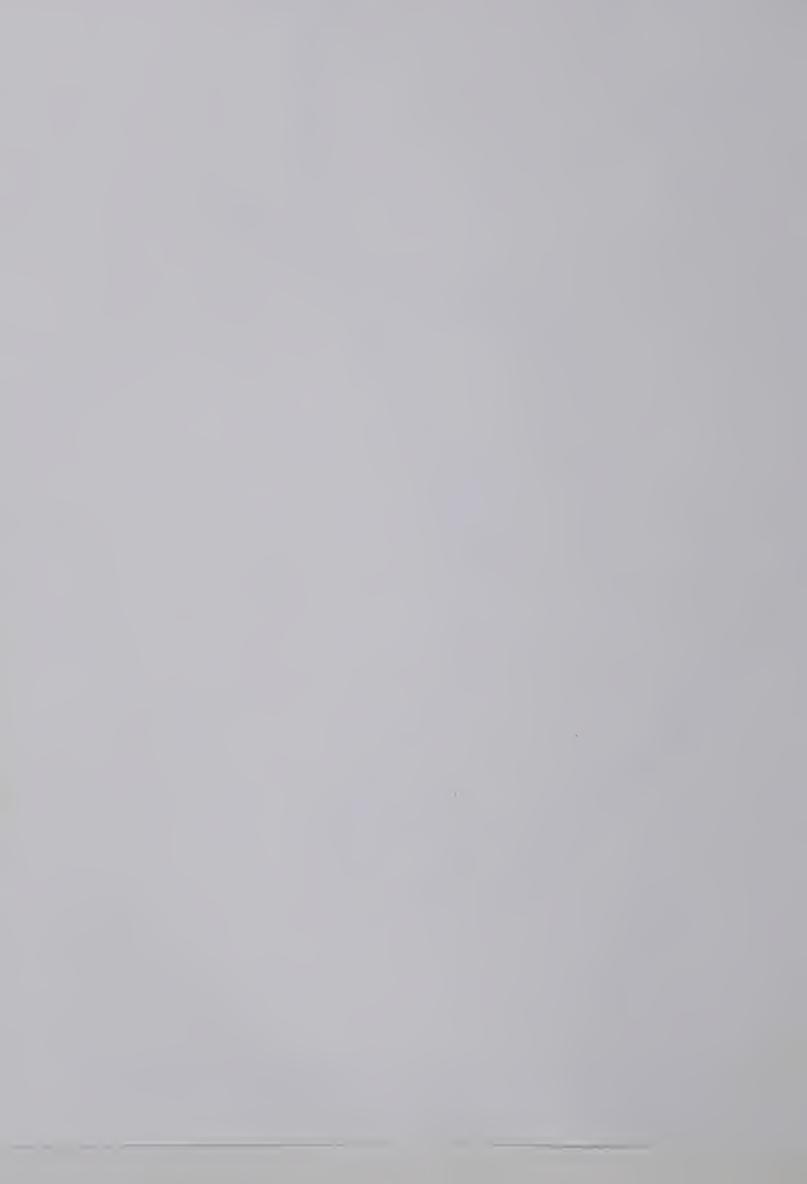for general maintenance of health.

Dogs weighing between ten and thirty kilograms were
selected for the experiments. It was felt that these
animals could tolerate blood sampling without signific-
antly depleting the blood volume.

On the day preceding an experiment the dog to be
used was not fed. It was anaesthetized with intravenous
Nembutal Sodium 30 mgm/kg; the neck and upper one-third
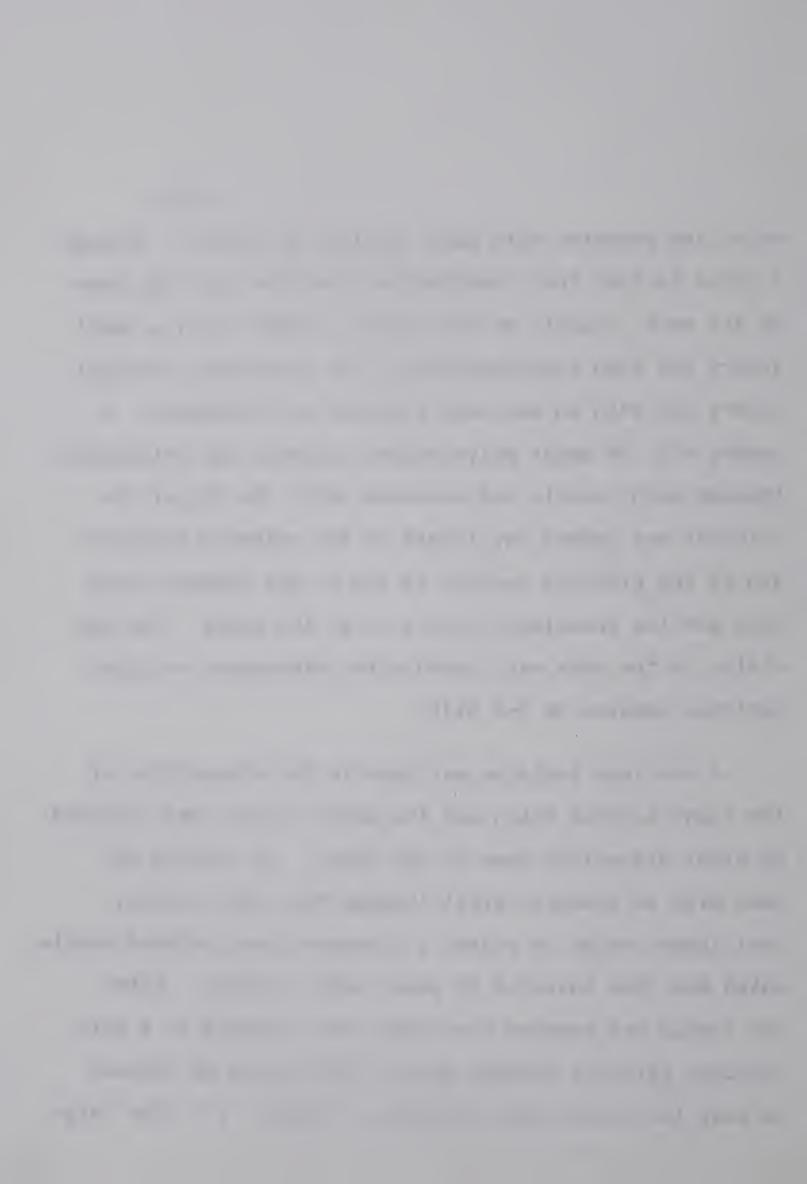of the chest were shaved, washed with surgical soap and

FEMUR

IGURE 4 Placement Of Femoral Marrow Catheter

water and prepared with pale tincture of iodine. Through
a three to four inch longitudinal incision over the base
of the neck, usually on the animal's right side, a small
artery and vein corresponding to the transverse cervical
artery and vein in man were isolated and litigated. A
number P.E. 90 gauge polyethylene catheter was introduced
through both vessels and advanced until the tip of the
catheter was judged (by length of the catheter inserted
and by the pressure record) to lie in the superior vena
cava and the innominate artery or in the aorta. The in-
cision in the neck was closed with interrupted vertical
mattress sutures of 3-O silk.

A one inch incision was made in the mid-portion of
the right lateral thigh and the muscle groups were divided
by blunt dissection down to the femur. An opening was
made with an electric drill through the outer cortex,
just large enough to accept a 13-gauge blunt pointed needle,
which was then inserted in place with a trocar. After
the trocar was removed the needle was attached to a poly-
ethylene catheter through which D 5%/S could be infused
to keep the needle from clotting. (Figure 3) The thigh

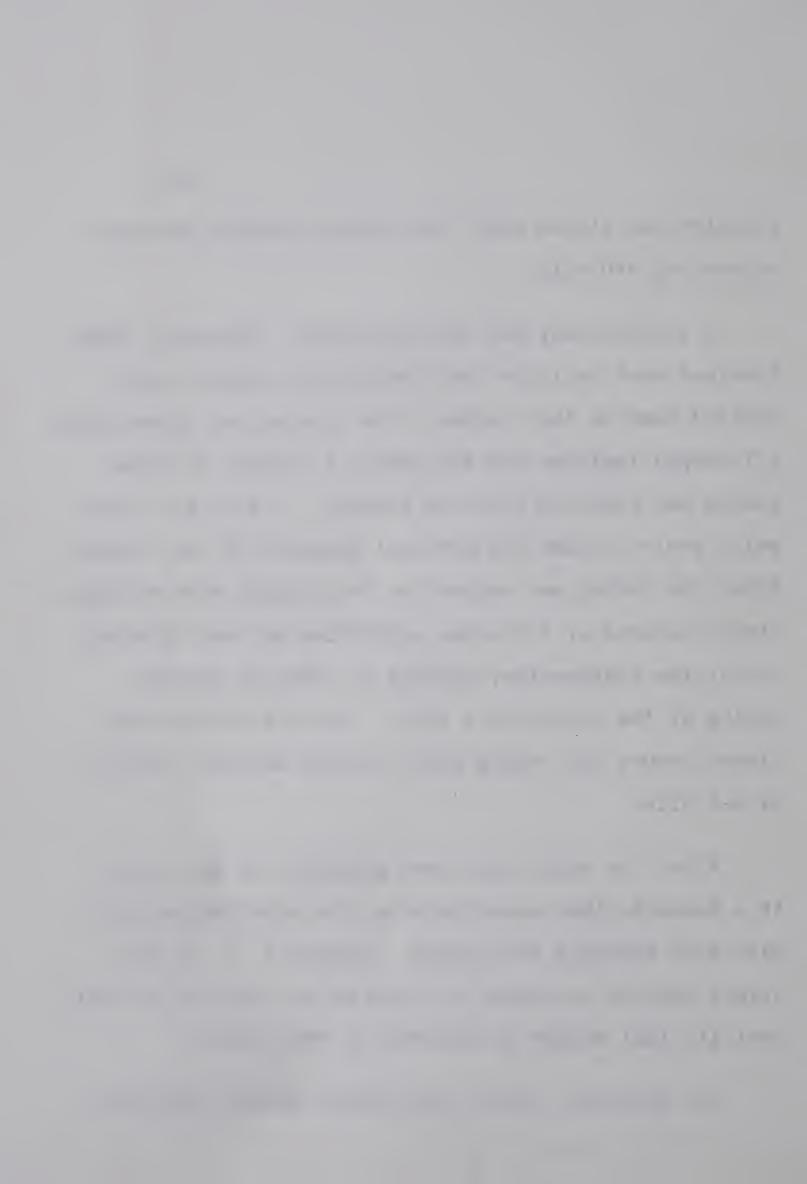FIGURE 5 Animal Harness : Placement Of Catheters In Neck

incision was closed with interrupted vertical mattress
sutures of 3-0 silk.

A tracheostomy was then performed. Through a long-
itudinal neck incision the subcutaneous tissues were
divided down to the trachea. The trachea was opened with
a T-shaped incision and the end of a section of tygon
tubing was inserted into the trachea. A size was chosen
which would occlude the internal diameter of the trachea.
After the tubing was sutured to the trachea with multiple
simple sutures of 3-0 silk, humidified air was directed
across the tracheostomy opening in order to prevent
drying of the respiratory tree. The neck incision was
closed around the tubing with vertical mattress sutures
of 3-0 silk.

After the animal had been prepared, it was placed
in a hammock-like canvas harness in a standing position
with feet touching the ground. (Figure 4) If the
animal desired to stand, it could do so, and yet it could
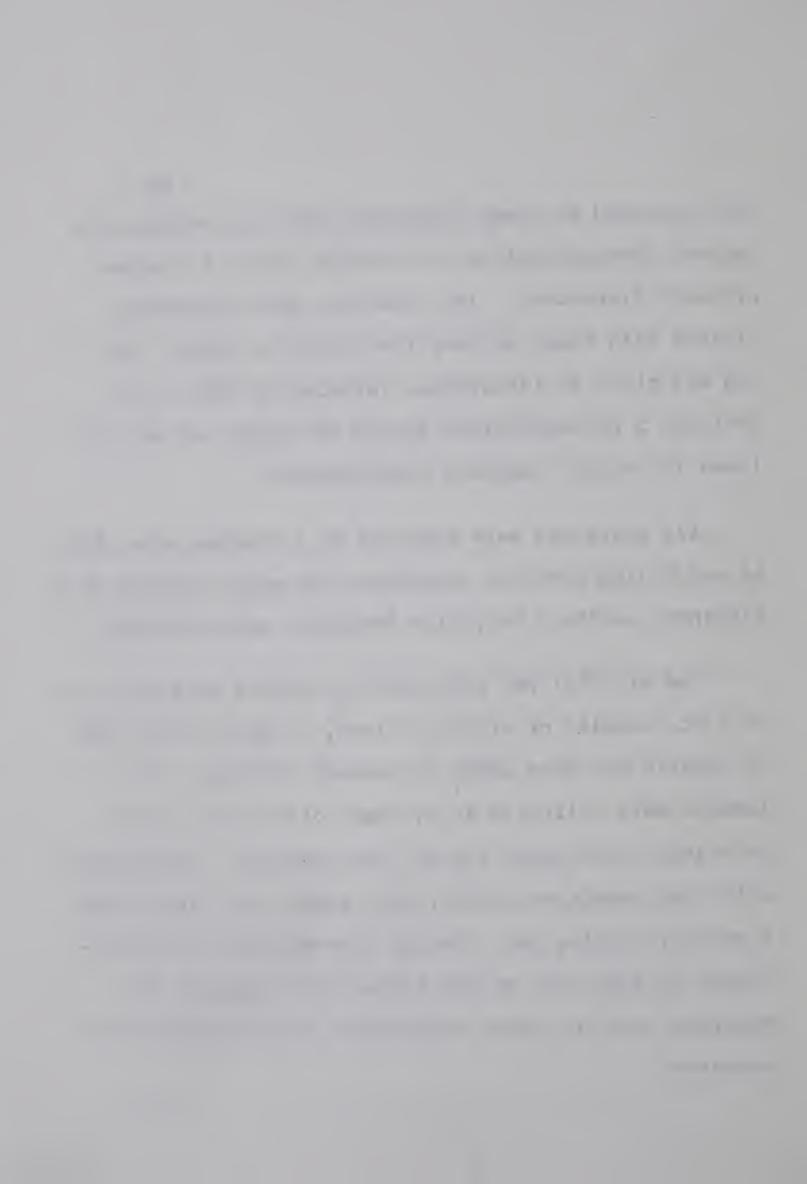rest its full weight as desired, in the hammock.

The arterial, venous and femoral marrow catheters

were attached by 3-way stopcocks both to a bottle of 5 percent Dextrose/Saline IV solution and to a Statham pressure transducer. The catheters were frequently flushed with fluid to keep them clear of clots. The dog was given an intravenous infusion of 1000 cc. of Dextrose 5 percent/Saline during the night and was allowed to recover complete consciousness.

All pressures were measured by a Statham model P23-AA and P23-BB pressure transducer and were recorded on a 4-channel Sandborn Poly-Viso Recorder, model 67-1200.

The arterial pH, pCO_2 and CO_2 content were measured on 3 cc. samples of arterial blood, to which three mgm. of Heparin had been added to prevent clotting. The samples were collected in syringes oiled with liquid petroleum, from which all air was excluded. Immediately after the sample was taken, the syringe was capped with a mercury sealing cap. The pH determinations were performed in duplicate on the Astrup Physiological Gas Analyzer, and the other values were obtained using the nomogram.
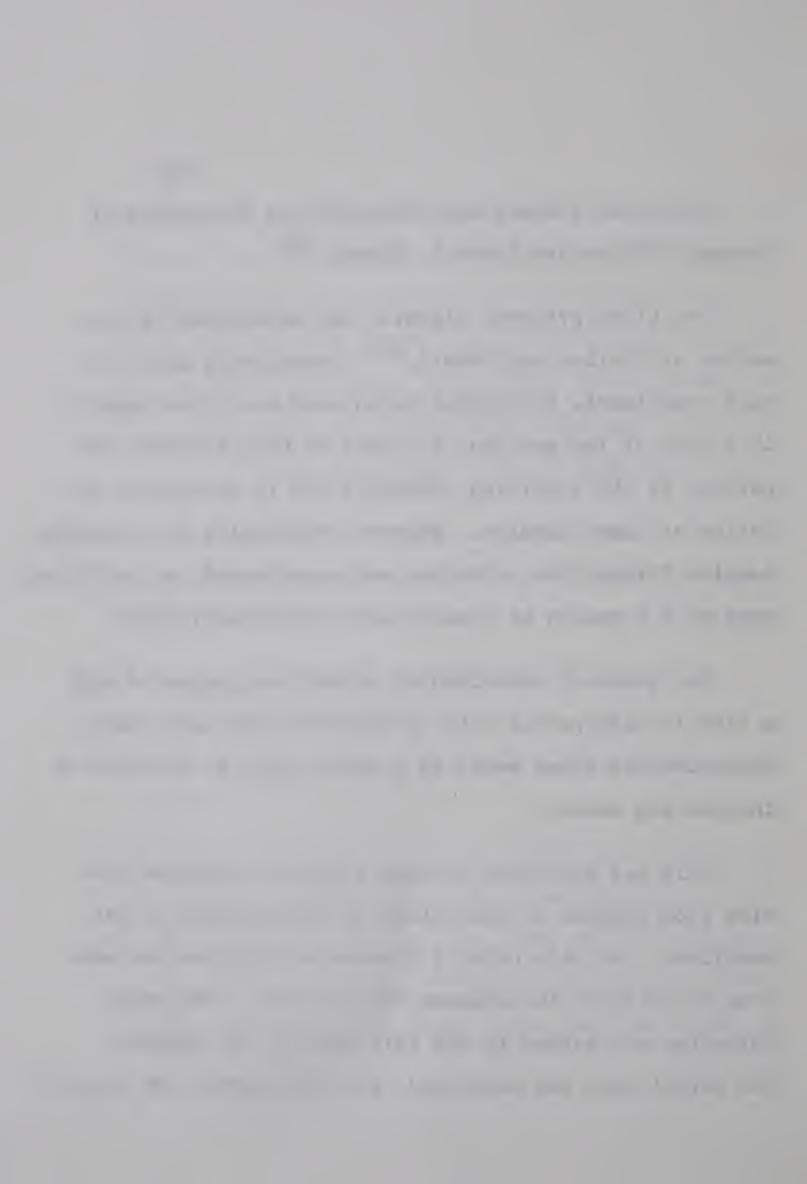
The blood lactate was determined by the method of
Donough O'Brien and Frank A. Ibbott.[128]

The blood pyruvate likewise was determined by the
method of O'Brien and Ibbott.[129] Immediately prior to
each experiment, the animal being used was given Heparin
in a dose of two mgm./kg. in order to help maintain the
patency of the recording catheters and to facilitate the
taking of blood samples. Whenever difficulty in obtaining
samples through the catheters was experienced, an additional
dose of 0.5 mgm/kg of Heparin was occasionally given.

One group of experimental animals was prepared with
a side to side portal vein to inferior vena cava shunt,
approximately three weeks to a month prior to the time of
introducing shock.

This was performed through a midline incision run-
ning from xyphoid to two-thirds of the distance to the
umbilicus. At this point a transverse incision was made
from one side of the abdomen to the other. The small
intestine was packed to the left side of the abdomen.
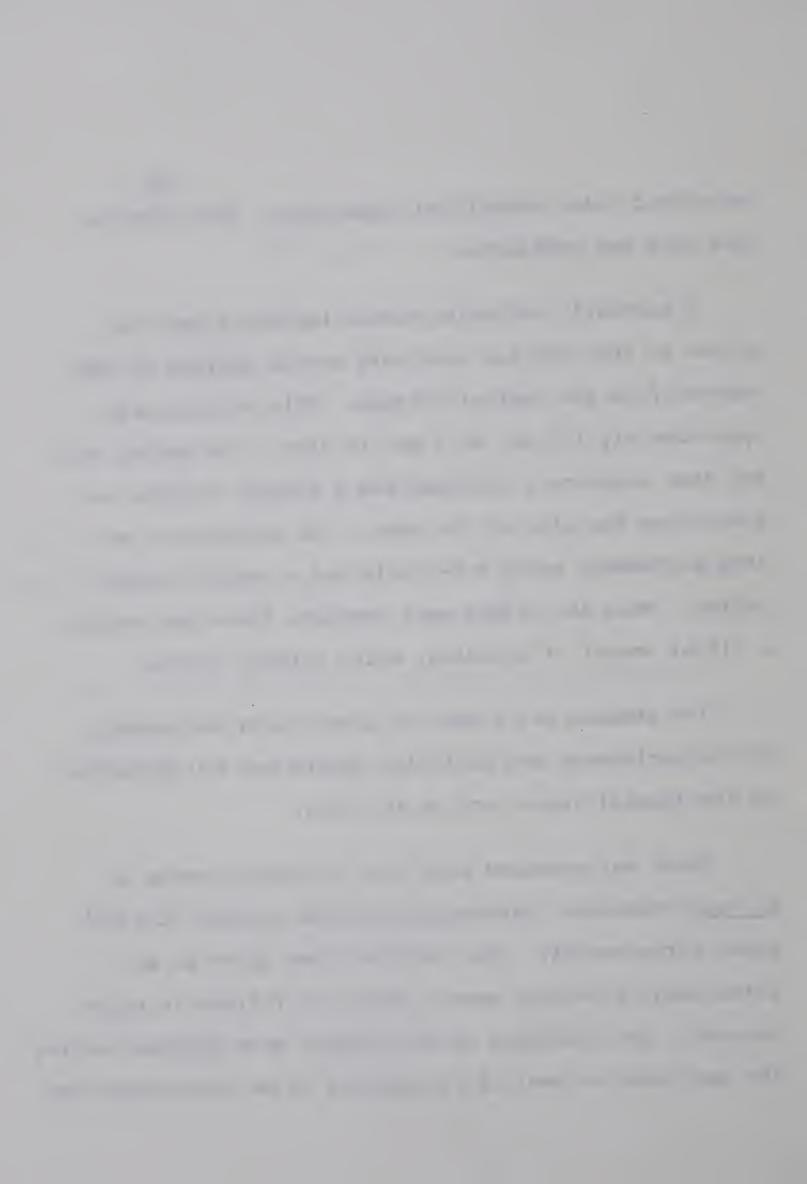The portal vein was mobilized, and the splenic and superior

mesenteric veins identified separately. The inferior
vena cava was mobilized.

A partially occluding curved bulldog clamp was
placed on the inferior vena cava and an ellipse of vein
removed from the ventral surface. This ellipse was
approximately 1.5 cm. by 7 mm. in size. The portal vein
was then completely occluded and a similar ellipse re-
moved from the side of the vein. The anastomosis was
then performed, using a 6-0 silk and a running simple
stitch. When the clamps were removed, there was usually
a slight amount of bleeding, which quickly ceased.

The abdomen was closed in layers with 3-0 chromic
on the peritoneum and posterior sheath and 4-0 dermalene
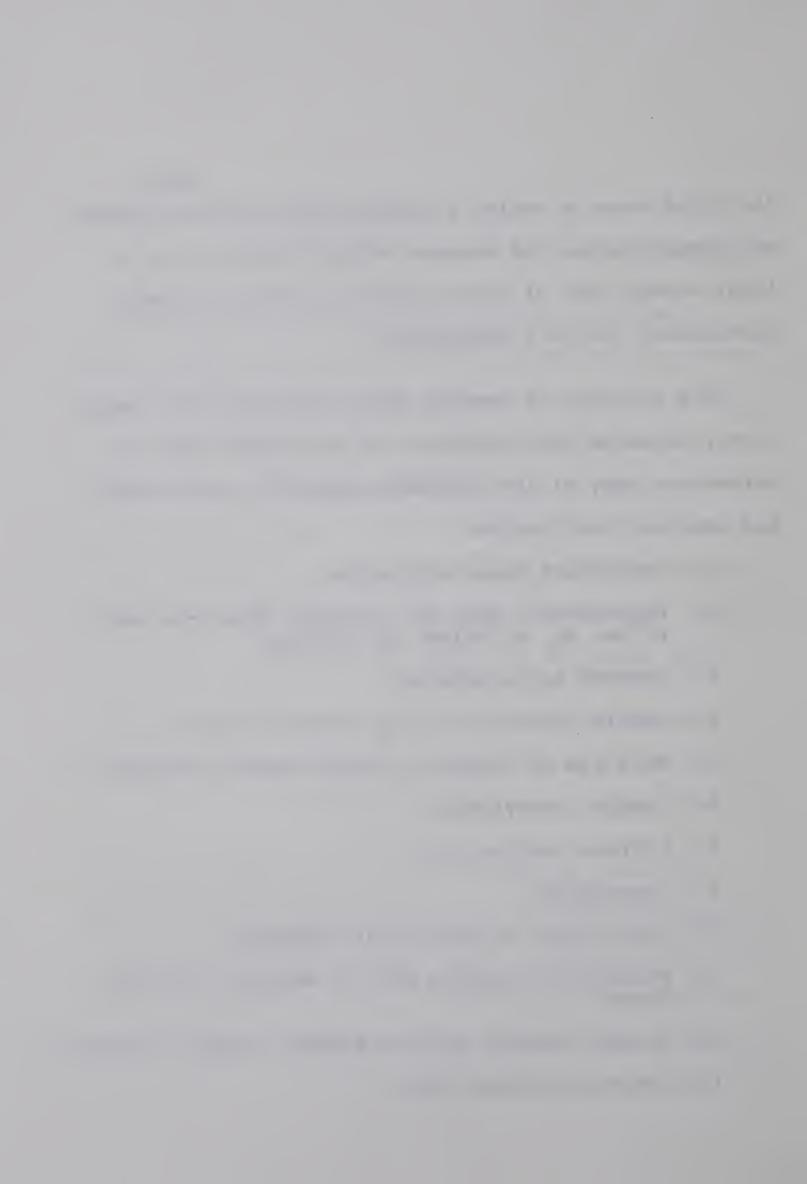on the fascial layers and on the skin.

Shock was produced with five to thirty mgm/kg of
E. coli endotoxin (bactopolysaccharide extract 0111-B4)
given intravenously. The endotoxin was given as an
intravenous injection over a period of fifteen to thirty
seconds. The reactions of the animals were observed during
the next hour or two; if it appeared to be recovering from

the first dose of toxin, a second dose (or even a third) was administered; the purpose being to ensure that a large enough dose of toxin had been received to make spontaneous recovery impossible.

For a period of several hours blood pressure, pulse rates, serum pH and bloodgases of the animal were recorded and many of the following signs of severe shock and imminent death noted:

1. Persistent hyperventilation.

2. Hypotension, with the systolic blood pressure 80 mm. Hg. or below and falling.

3. Reduced pulse pressure.

4. Severe reduction in CO_2 content or pH.

5. Very low or negative central venous pressure.

6. Cardiac arrhythmias.

7. Extreme restlessness.

8. Convulsions.

9. Respiration or heart beat stopping.

10. Persistent vomiting with or without contained blood.

11. Bloody diarrhea with or without strips of mucosa.

12. Increasing hematocrit

Other signs peculiar to the porto-caval shunt dogs were:

1. A terminal hypertensive episode.

2. The presence of Meyer Waves in the blood pressure tracing.

Treatment was started when the animal showed a combination of several of the above signs. A description of the treatment will be outlined later. The methods of preparation of medications and dosages were as follows:

Plasma Expander:

Tyrode's solution was made, having the following composition:

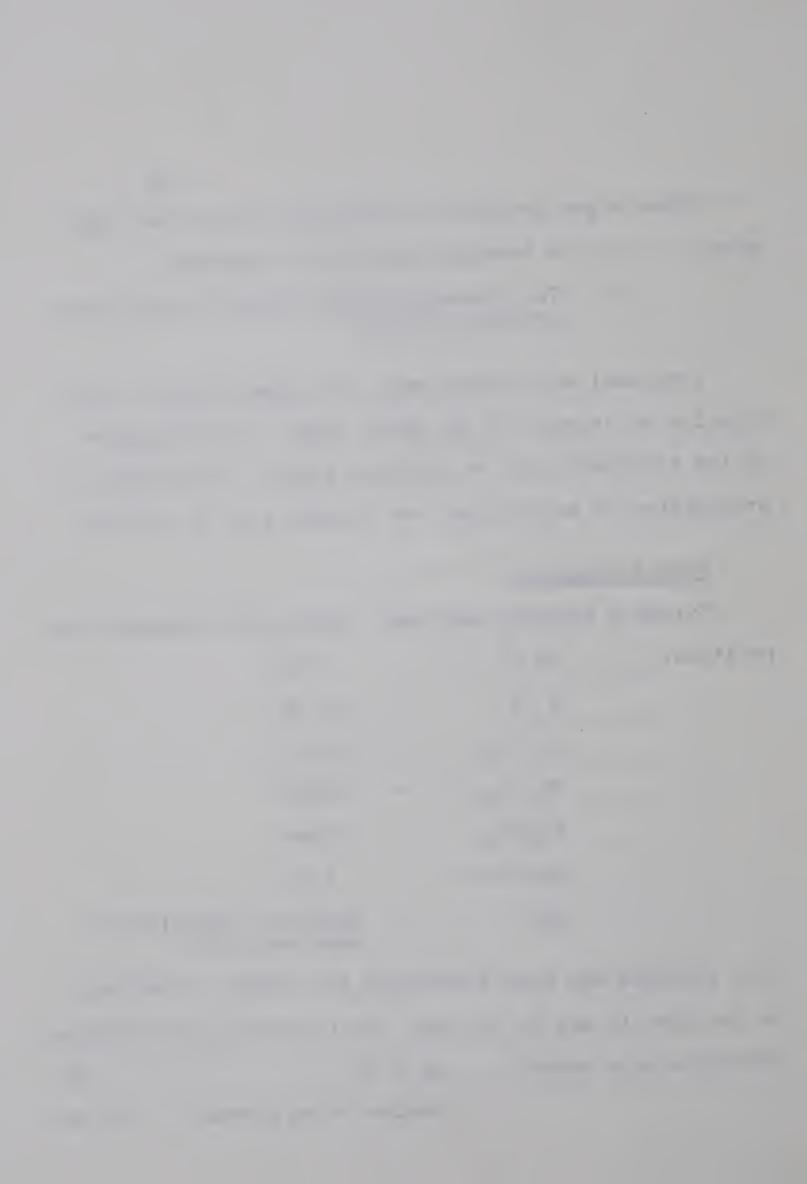|		
Na Cl	-	8 gm.
K Cl	-	0.2 gm.
Ca Cl_2	-	0.2 gm.
Mg Cl_2	-	0.01gm.
KH_2PO_4	-	0.05gm.
Dextrose	-	1 gm.
H_2O	-	quantity sufficient to make one liter.

This solution was heat sterilized and stored. Just prior to the time it was to be used, the following non-sterilized solutions were added:

Na H CO_3	-	1 gm.
Bovine Serum Albumin	-	60 gm.

For each experiment, the blood volume of the animal was estimated to be one-tenth of the animal's weight in kilograms. During treatment, an amount of the plasma volume equal to fifteen percent of the estimated blood volume was given initially, and further amounts of volume expander were given as required to stabilize the blood pressure.

Dibenzylene Solution:

Phenoxybenzamine (Dibenzylene) was dissolved in Dextrose 5 percent water to make a final concentration of 1 mgm per cc. This solution was then infused intra-arterially over a period of thirty minutes, to a total dose of 1 mgm/kg of body weight.

Sodium Bicarbonate Solution:

One hundred and twelve gm. of $Na H CO_3$ was dissolved in a liter of sterile water to make a 1 Molar solution of sodium bicarbonate. At the time of treatment, an amount of this solution was infused intra-arterially to contribute 1.1 mgm. of $Na H CO_3$ for every minute during which the animal had been in shock, multiplied by one-third of the animal's weight in kilograms. This figure, which was arrived
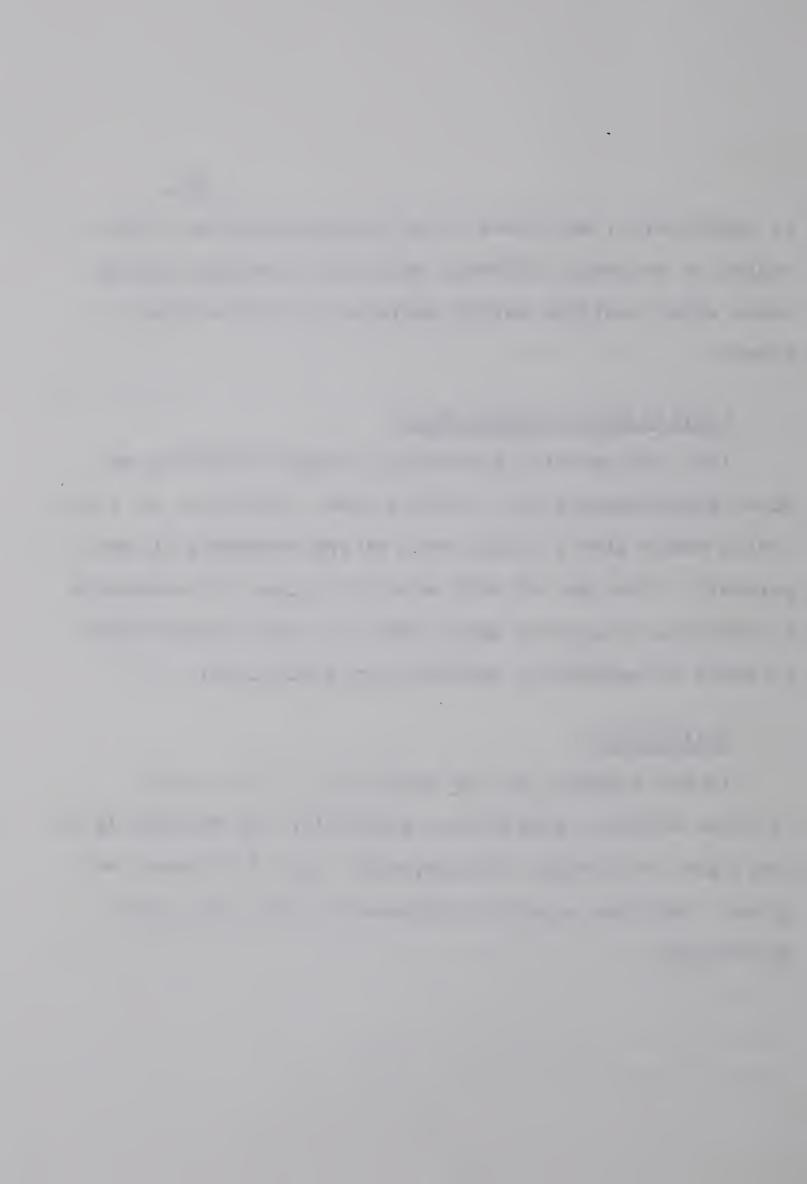
at empirically, was found to be an approximation of the degree of metabolic acidosis which had developed during shock which could be safely buffered by sodium bicarbonate.
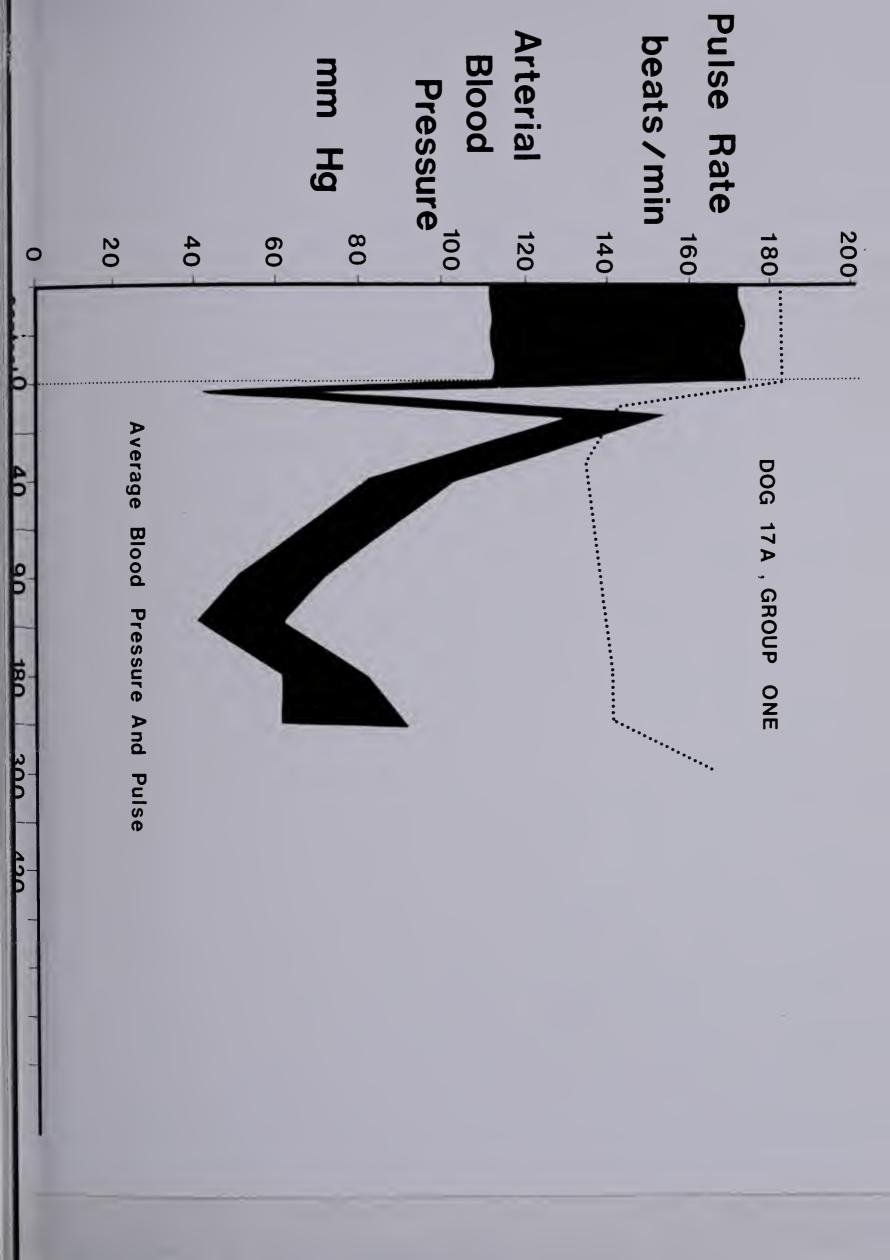
Epsilon Amino Caproic Acid:

This non-specific proteolitic enzyme inhibitor was given intravenously in a loading dose, initially, of 1 gm. (which would give a blood level of approximately 15 mgm. percent). Four gm. of EACA were then given intravenously in Dextrose 10 percent water 1000 cc. every twelve hours in order to maintain a satisfactory blood level.

Antibiotics:

In all animals, at the conclusion of the resuscitation efforts, intravenous penicillin one million U$\bar{q}$ 12 hours and intravenous chloromycetin 1 gm. $\bar{q}$ 12 hours was given. This was usually continued for five days postoperatively.

Pulse Rate
beats/min

Arterial
Blood
Pressure

mm Hg

DOG 17A, GROUP ONE

Average Blood Pressure And Pulse

RESULTS:

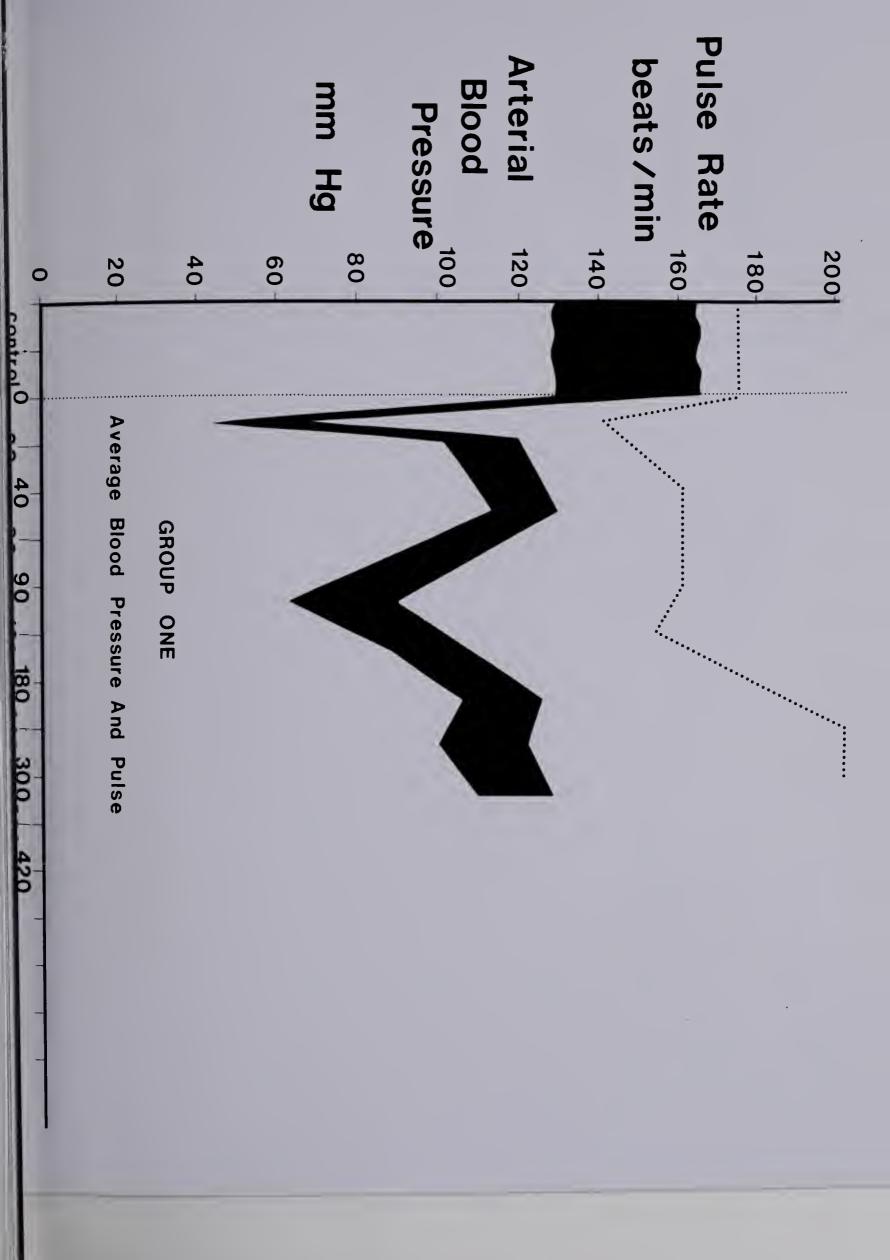## Physiological Changes, Normal Animals

The first observations were made on groups of dogs (Group one) previously anaesthetized with Nembutal 30 mgm/kg. I.V. These dogs were given five mgm/kg. of endotoxin I.V. and the blood pressure, pulse rate, clinical course and survival were noted in order to compare the experimental program to the previously reported work of other groups.[19,48,125]

Clinical behaviour was similar to that recorded by others. There was an immediate marked drop in blood pressure, followed by a gradual return to approximately three-quarters of the initial pressure and stabilization at this point. A second fall in blood pressure then developed slowly and continued for several hours until death or recovery occurred. The animal's tongue and gums were noted to be cyanotic, and copious salivation occurred. Mild diarrhea was common, and occasional bloody diarrhea occurred late in shock.
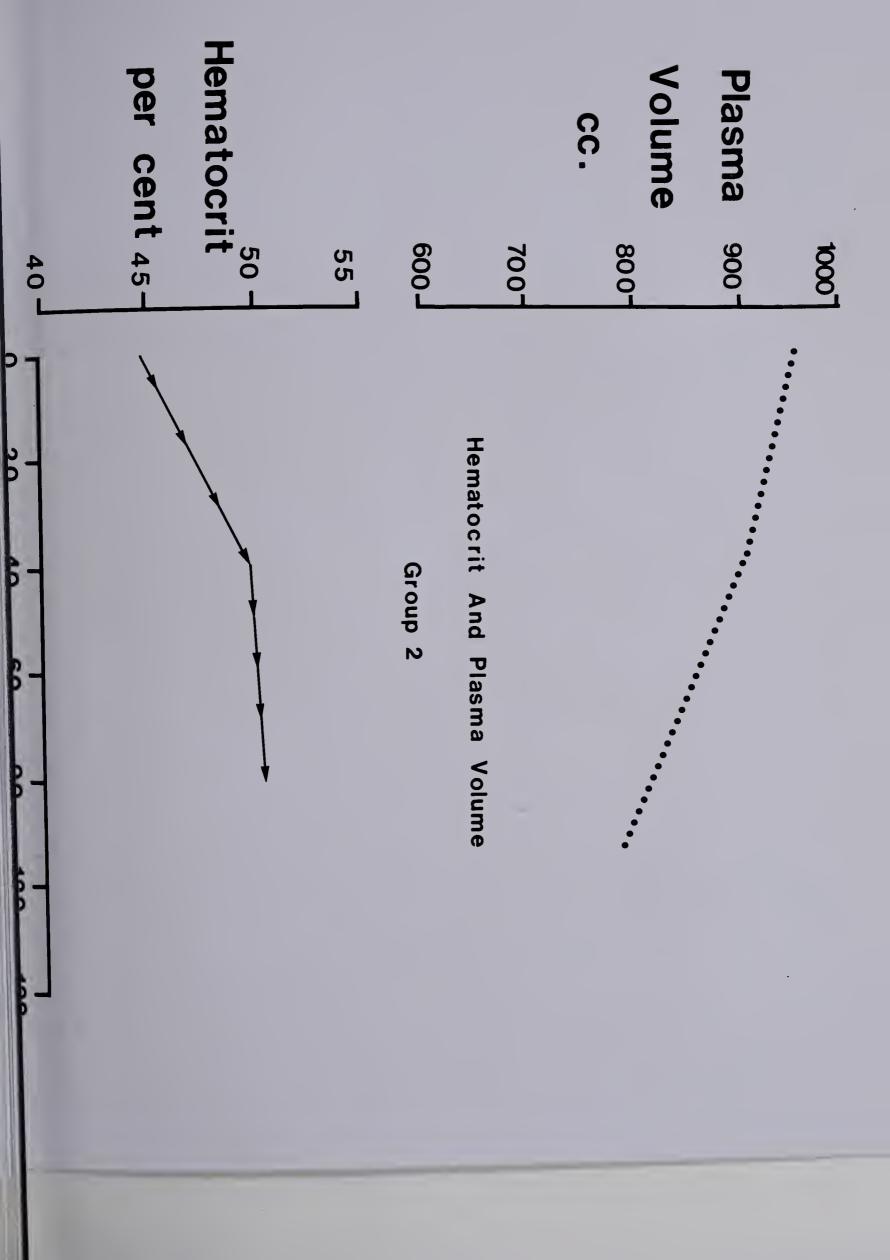
A typical blood pressure and pulse record is shown in Figure 5. The average of all animals is shown in

Pulse Rate
beats/min

200 180 160 140

Arterial
Blood
Pressure

mm Hg

120 100 80 60 40 20 0

control 0

40   90   180   300   420

GROUP ONE

Average Blood Pressure And Pulse

Plasma
Volume
cc.

1000
900
800
700
600

Hematocrit And Plasma Volume

Group 2

Hematocrit
per cent

55
50
45
40

0   20   40   60   80   100

pH, pCO$_2$, And Total CO$_2$

Group 2
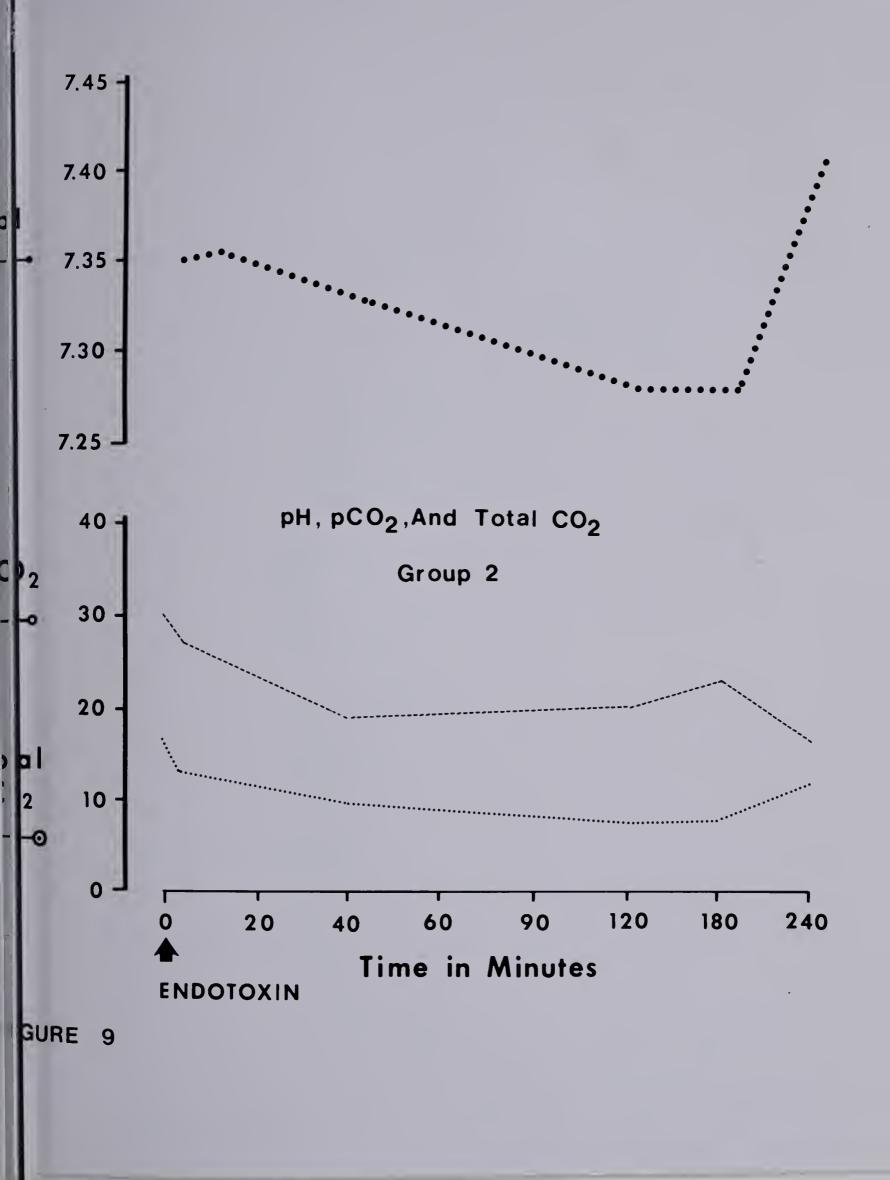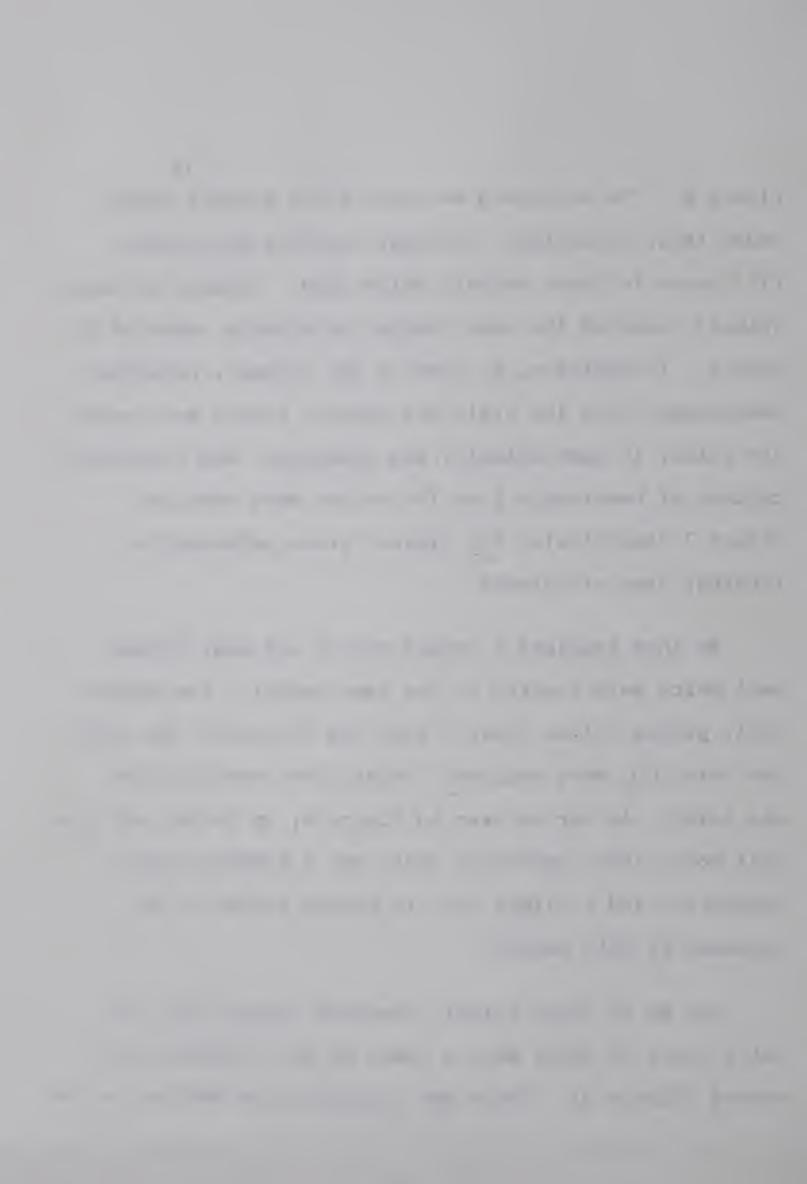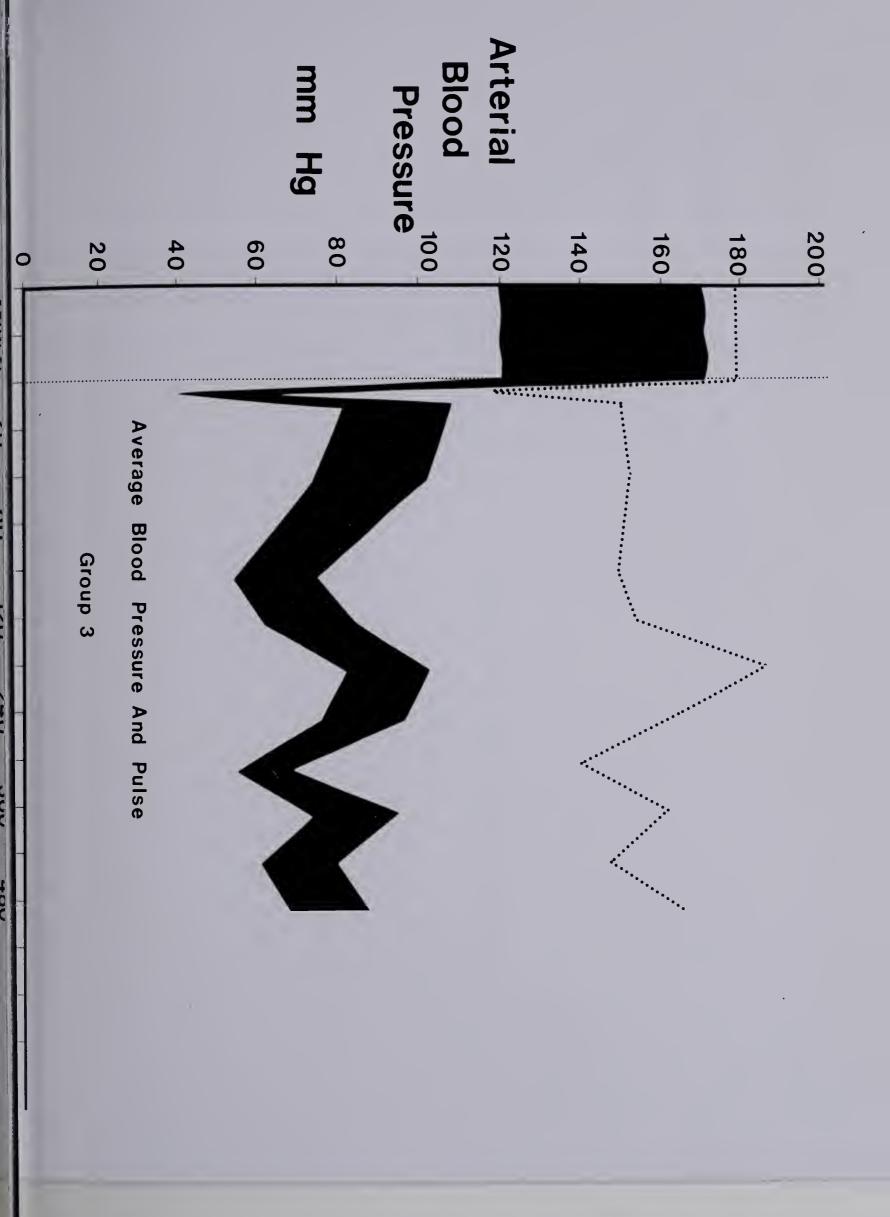
Time in Minutes

ENDOTOXIN

FIGURE 9

Figure 6. The endotoxin was only fifty percent lethal under these conditions. Average survival was eleven (11) hours in those animals which died. Autopsy of these animals revealed the same changes previously reported by others. In addition, in some of the animals, petechial hemorrhages into the brain and adrenal tissue were noted. The colon, in some animals, was edematous, and occasional patches of hemorrhage into the mucosa were observed. Figure 7 demonstrates the typical gross pathological findings seen at autopsy.
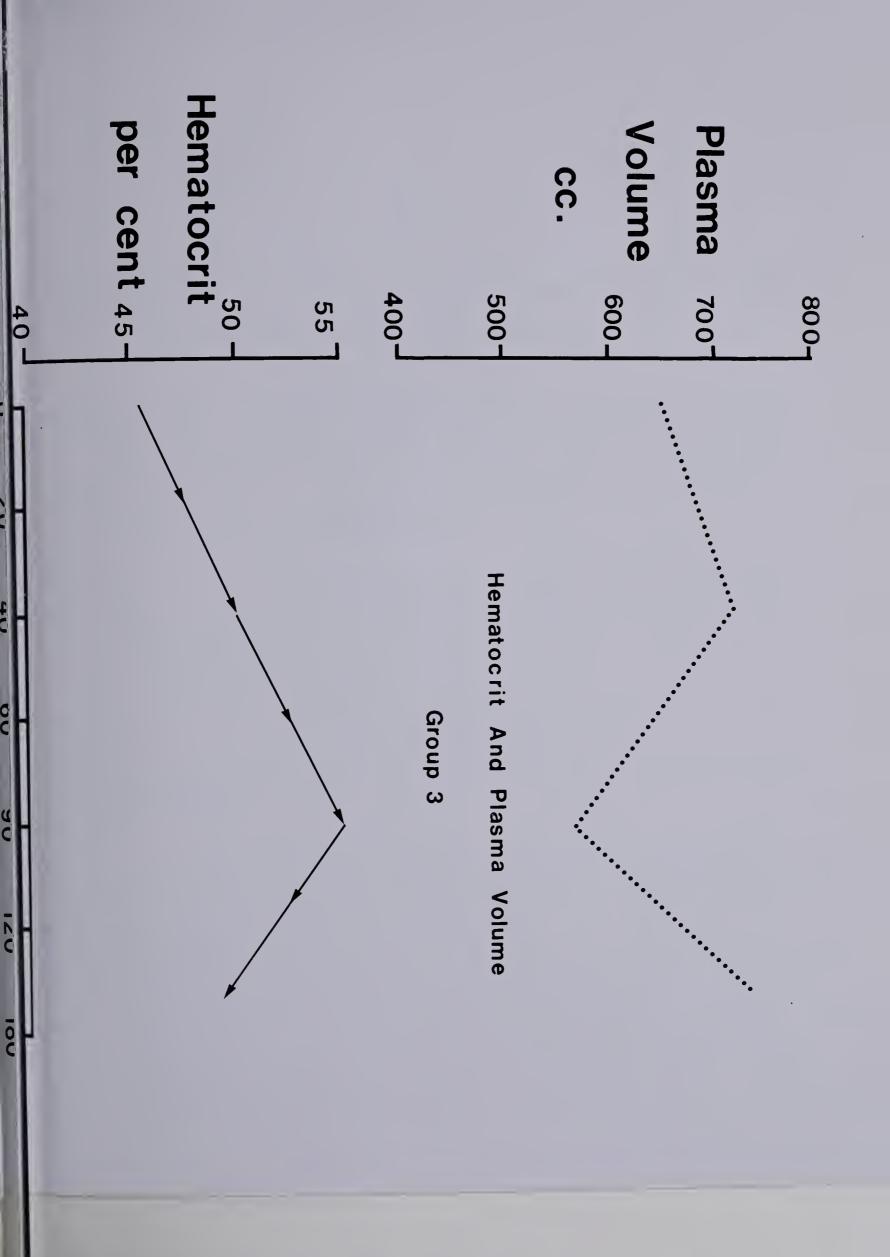
We then examined a second set of six dogs (Group two) which were treated in the same manner. The hematocrit, plasma volume (Evan's blue dye dilution), pH, pCO_2 and total CO_2 were measured. Again the survival time was noted. As can be seen in Figure 8, up to one and one-half hours after endotoxin there was a gradual rise in hematocrit and a slight fall in plasma volume as determined by this method.

The pH of these animals remained normal until the later hours of shock when a lower pH was frequently observed (Figure 9). There was a progressive decline in the
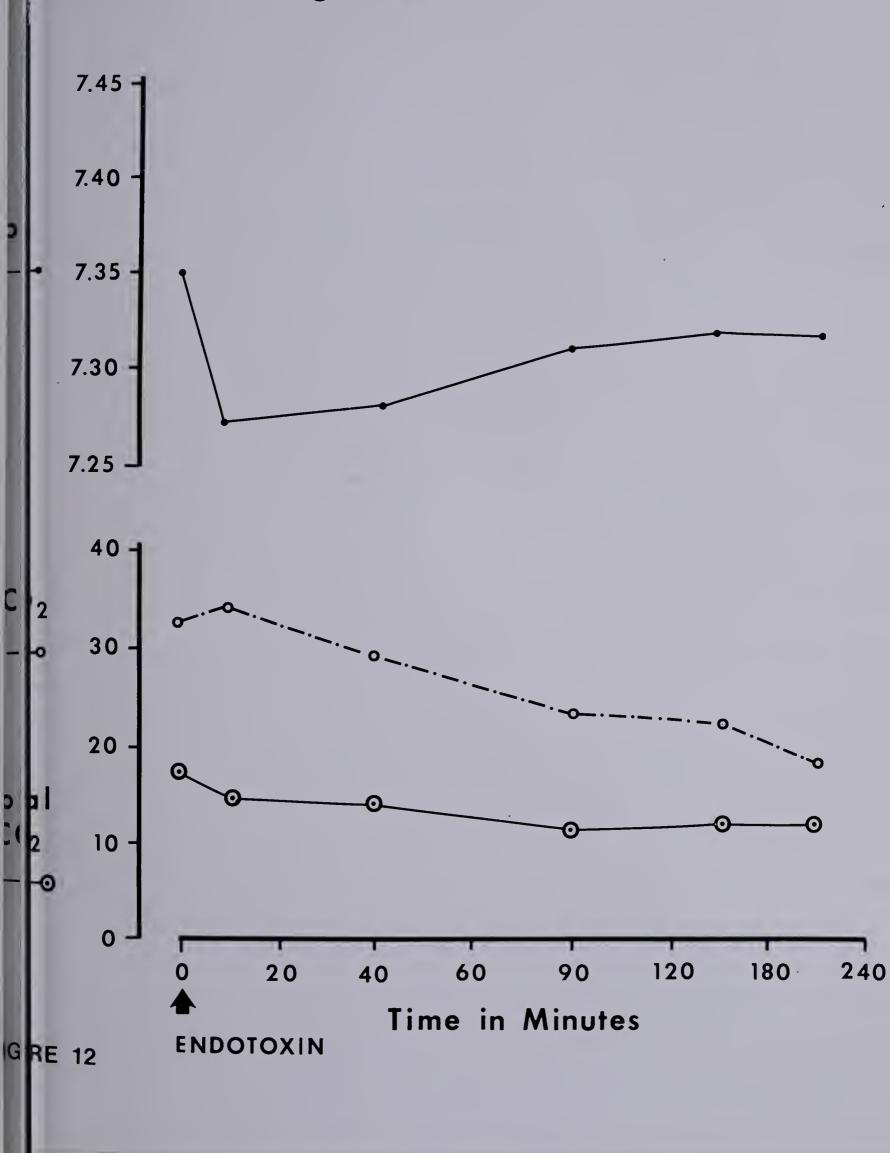
Arterial Blood Pressure
mm Hg

Average Blood Pressure And Pulse

Group 3

Plasma
Volume
cc.

800
700
600
500
400

Hematocrit And Plasma Volume

Group 3

Hematocrit
per cent

55
50
45
40

pCO_2 and total CO_2 indicating the development of a sig-
nificant degree of metabolic acidosis.

In this group, again, the dose of endotoxin used
was not uniformly lethal. Thirty-three percent of the
dogs survived. The survival time was eleven and one-
quarter hours, on the average.

In a group of sixteen dogs (Group three) the above
observations were confirmed, and the observations were
continued over a longer period of time. It can be seen
from Figure 10 that the average blood pressure recordings
of these animals followed the same pattern as previously
described.

The hematocrit increase up to one and one-half hours
of shock was again observed, but there tended to be a
consistent return toward a normal value at two and one-
half hours. Similarly, the plasma volume was noted to
show a decrease of variable degree at one and one-half
hours and a return to a relatively normal value at two
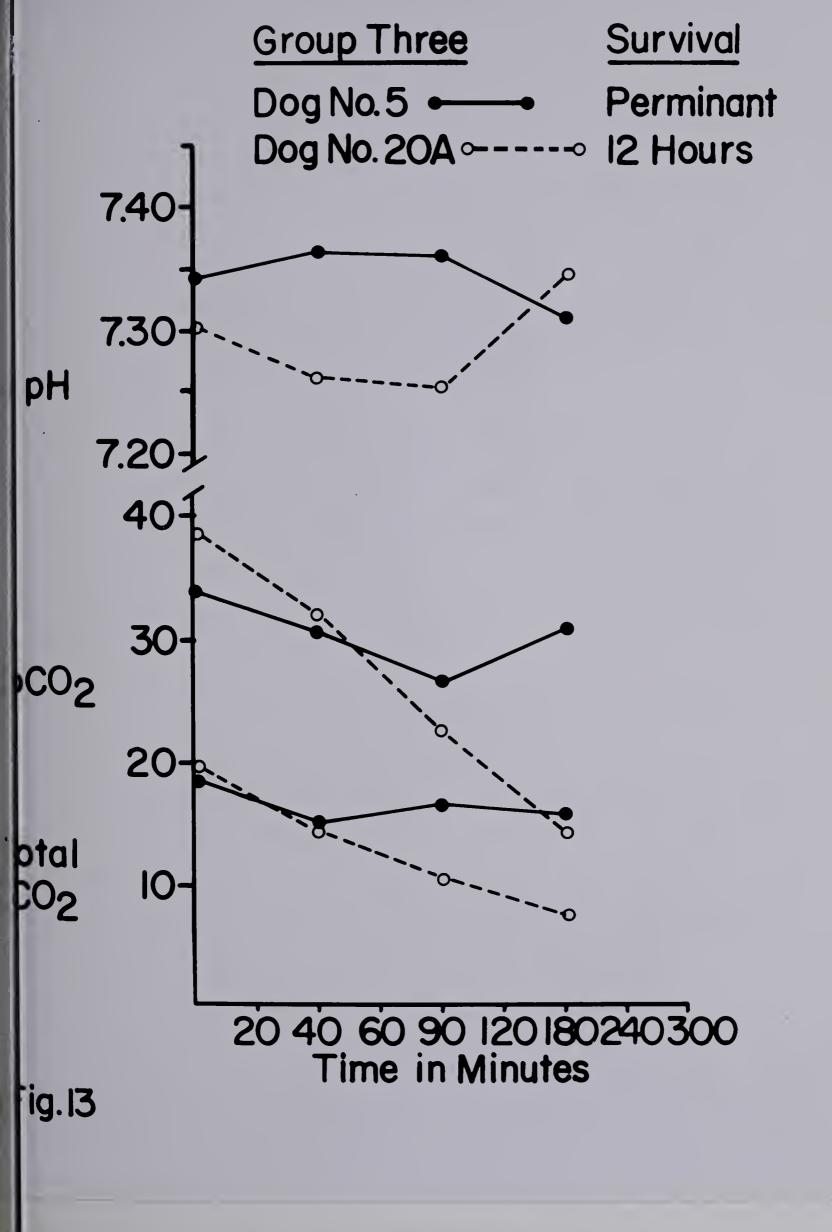and one half hours of shock. (Figure 11)

Average Values:

ENDOTOXIN

Time in Minutes

FIGURE 12

The pH in this larger group of animals also showed a variable drop. There was a consistent decrease in the pCO_2 and the total CO_2, again demonstrating a significant degree of metabolic acidosis. These findings are illustrated in Figure 12.

In this group of sixteen animals there were three permanent survivors, and the average survival was seventeen and three-quarter hours.

The clinical course of these animals and the autopsy findings were in every respect similar to those already described.

It should be emphasized that the average values for pH, pCO_2 and total CO_2 in the later hours of shock are consistently higher than those seen in later experiments. This occurs primarily because those animals which ultimately survived the shock process were returning toward normal values at these times. Individual animals which ultimately died showed a more profound degree of metabolic acidosis.

Fig. 13

A comparison of the results from two animals, one a survivor and the other a fatal case, are presented to illustrate this point in Figure 13.

In all of these animals, oliguria or anuria was consistently observed. The animal usually emptied its bladder spontaneously following the administration of endotoxin. From this point on until death the most urine produced by any animal was eleven cc. per hour, and this level of output was rarely observed.

Because of suggestions in the literature that barbiturates modified the clinical course of shock, it was decided to perform all further experiments on the unanesthetized animal.[119] Catheters for recording, sampling and infusing were inserted, as described, under nembutal anaesthesia the day prior to an experiment and the animal was allowed to regain consciousness.
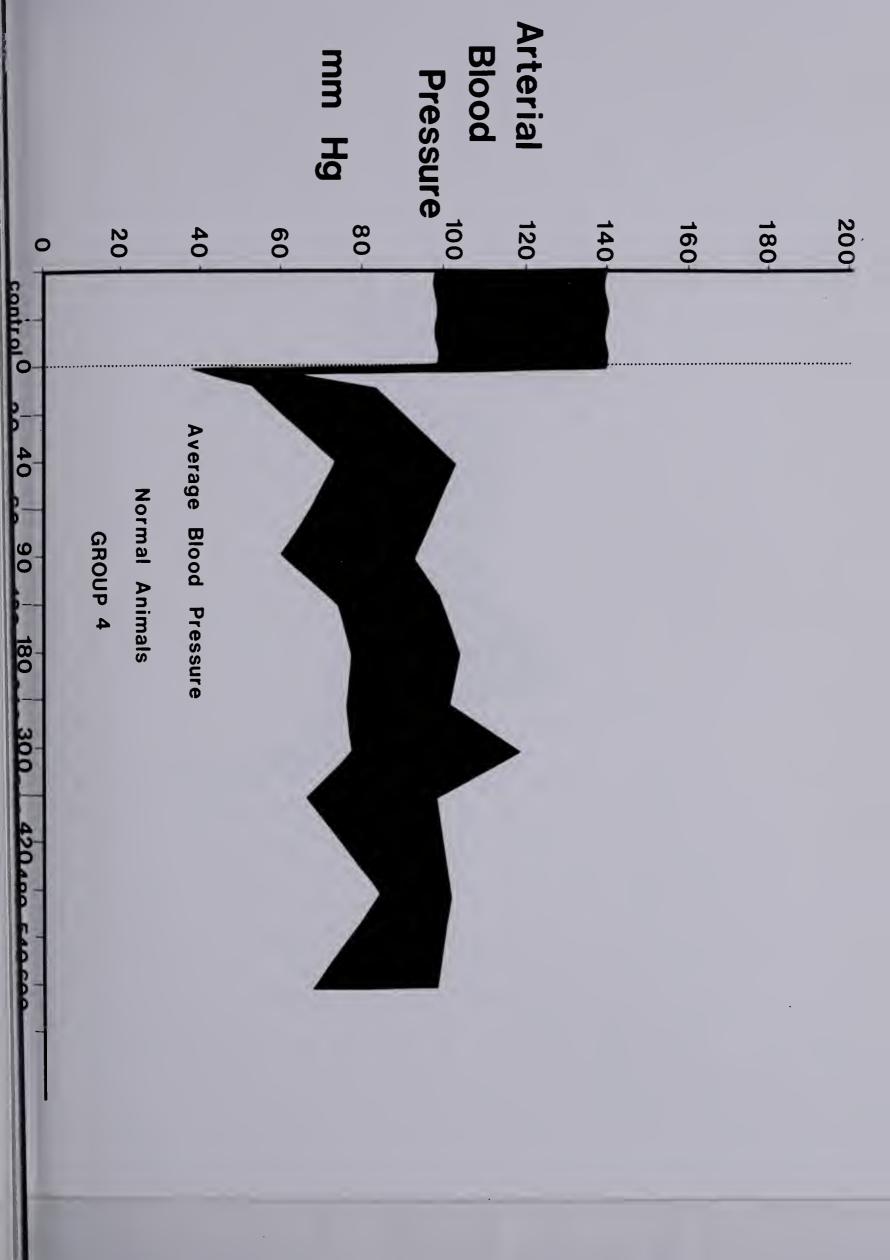
Sixteen animals were subjected to shock with endotoxin in the non-anaesthetized state (Group four). Blood pressures and pulse rates were monitored as were the pH, pCO_2, and total CO_2. If the animal seemed to be re-
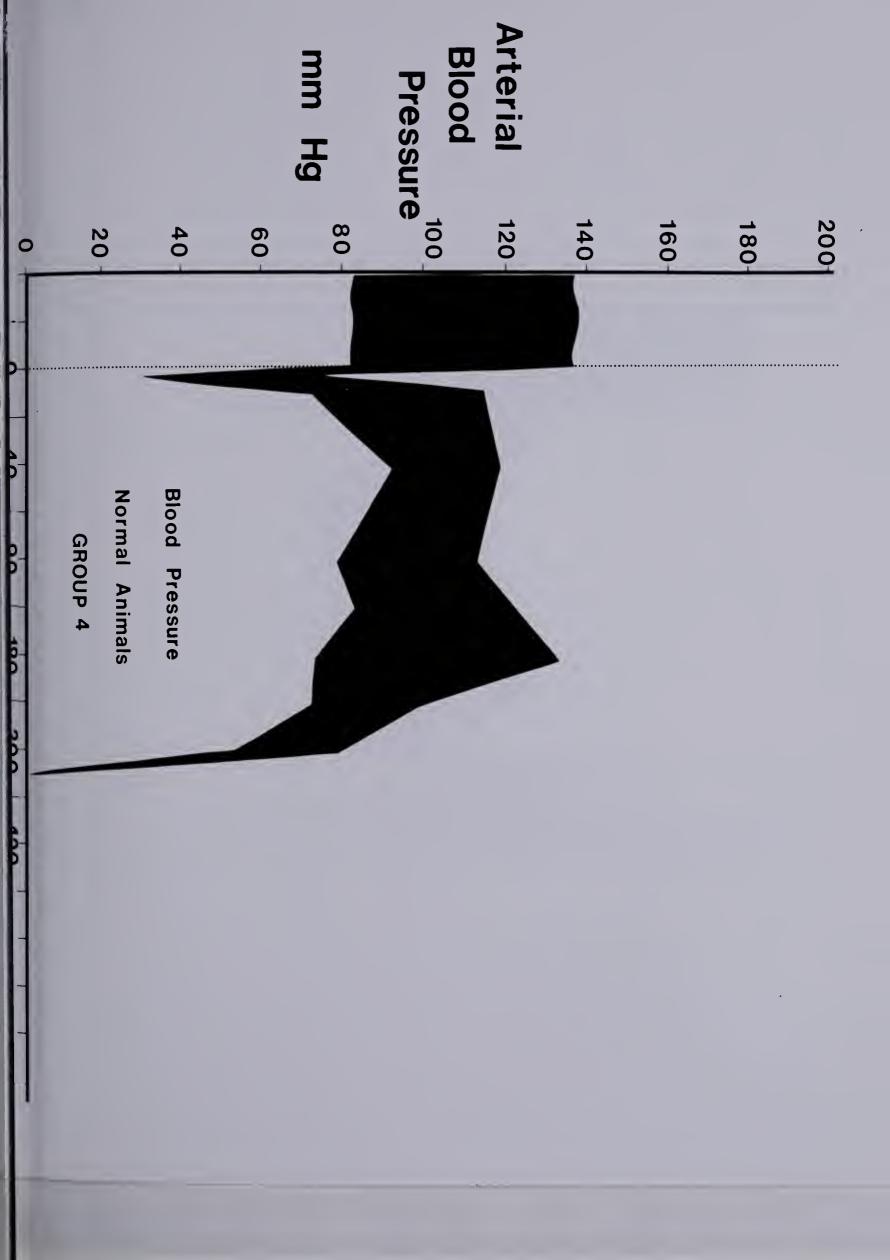
covering from the effects of the first dose of toxin,
further doses were given intravenously to increase the
severity of the animal's condition. The changes in these
animals were recorded until death occurred.

The average length of survival following endo-
toxin administration was ten and one-half hours, only
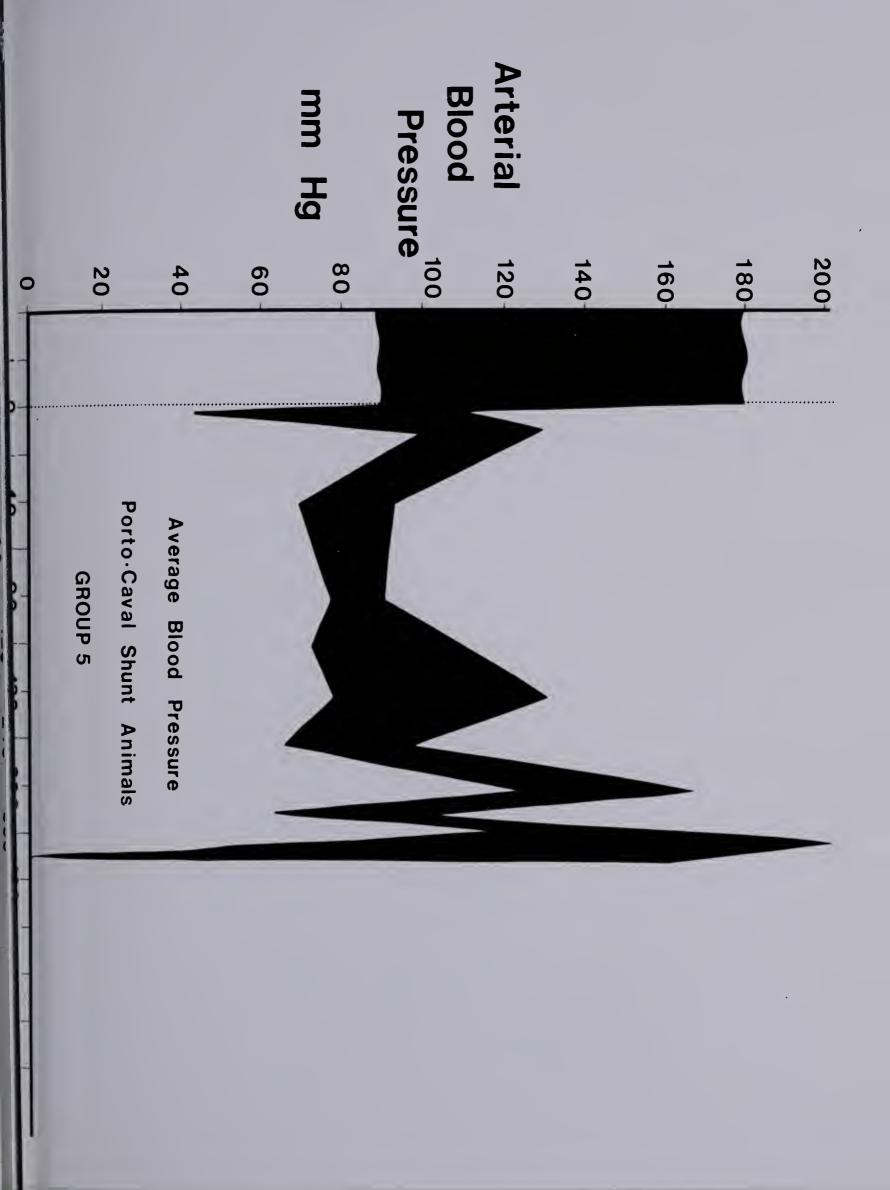slightly less than was observed with the anesthetized
dogs.

A more violent reaction following the injection of
endotoxin was observed in these animals. The animal was
apprehensive, struggled violently, developed hyperpnea
and had immediate urination and defecation. The animal
frequently vomited, and tenesmus and retching were common
throughout the entire course of the shock period. Lacri-
mation and salivation of marked intensity occurred and
conjunctival edema and engorgement of vessels was con-
stantly observed. The tongue and paws became quite cy-
anotic in most cases and subcutaneous edema of the paws
or over the back was frequent. With the passage of time,
diarrhea became marked and blood, melena and strips of

Arterial Blood Pressure

mm Hg

Average Blood Pressure

Normal Animals

GROUP 4

Arterial Blood Pressure

mm Hg

200 180 160 140 120 100 80 60 40 20 0

Blood Pressure

Normal Animals

GROUP 4

Arterial Blood Pressure

mm Hg

Average Blood Pressure
Porto·Caval Shunt Animals

GROUP 5

mucosa appeared in the stool. These dogs were noted
to have an average of four loose or bloody stools each,
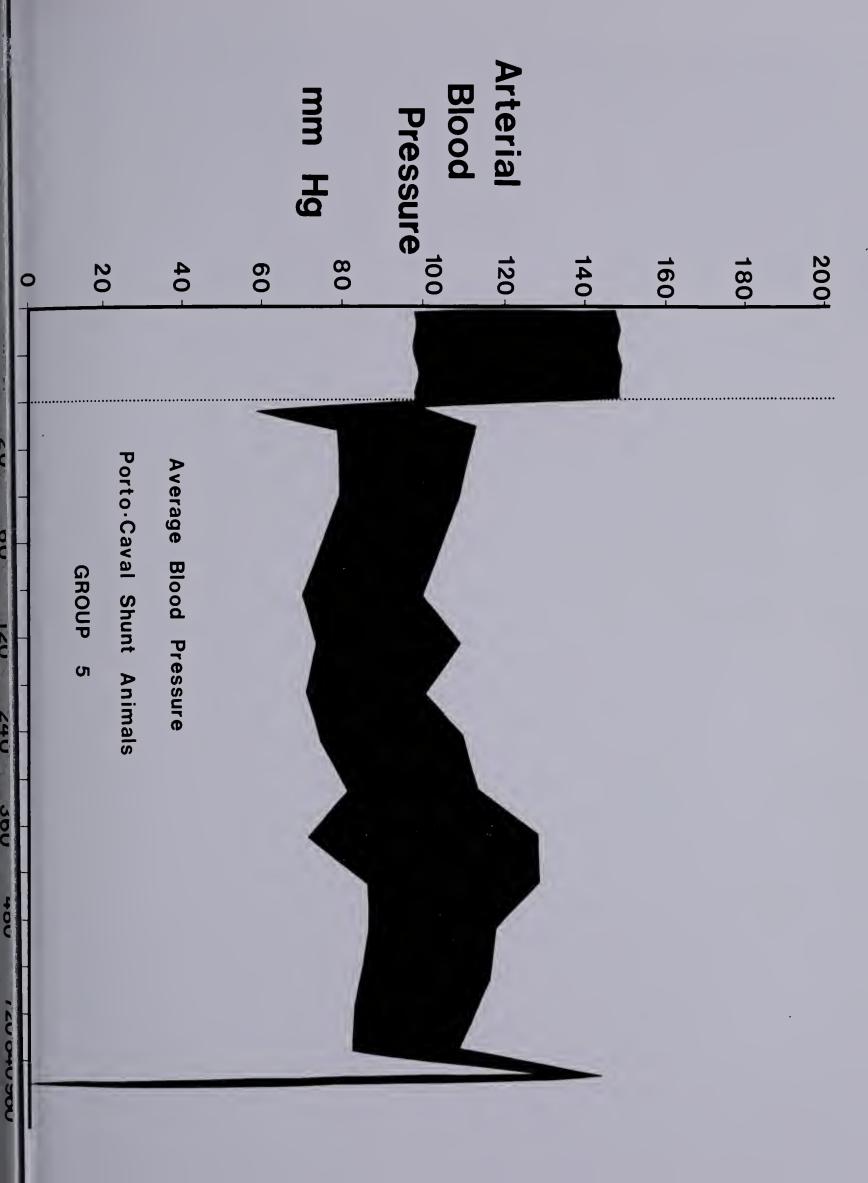prior to death.

The blood pressure response (Figure 14) was similar
in all respects to the records previously obtained in
anaesthetized dogs. The initial blood pressures in these
animals were generally lower than those noticed under
anaesthesia. This has been previously reported as a
property of barbiturates.

Physiological Changes, Porto-Caval Shunt Animals

A group of animals (seven dogs) previously prepared
with a porto-caval shunt were then similarly studied
during shock (Group five). (The patency of these shunts
subsequently proven at autopsy). There was a difference
in the blood pressure changes in this group of dogs which
is illustrated by a typical record in Figure 15. A "normal"
blood pressure tracing is included for comparison. (Figure
16).

These dogs showed only a gradual downhill trend of
the blood pressure immediately following endotoxin and
the subsequent stabilization of the blood pressure at a

Arterial Blood Pressure

mm Hg

Average Blood Pressure
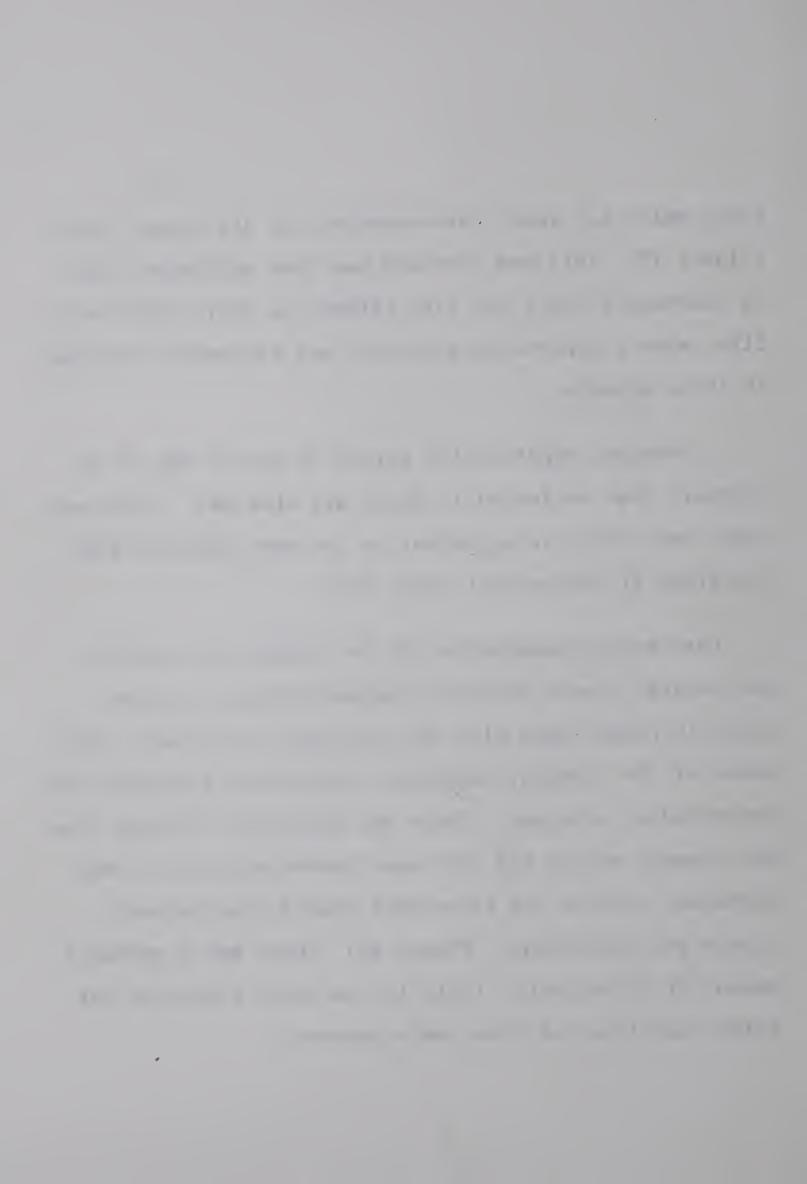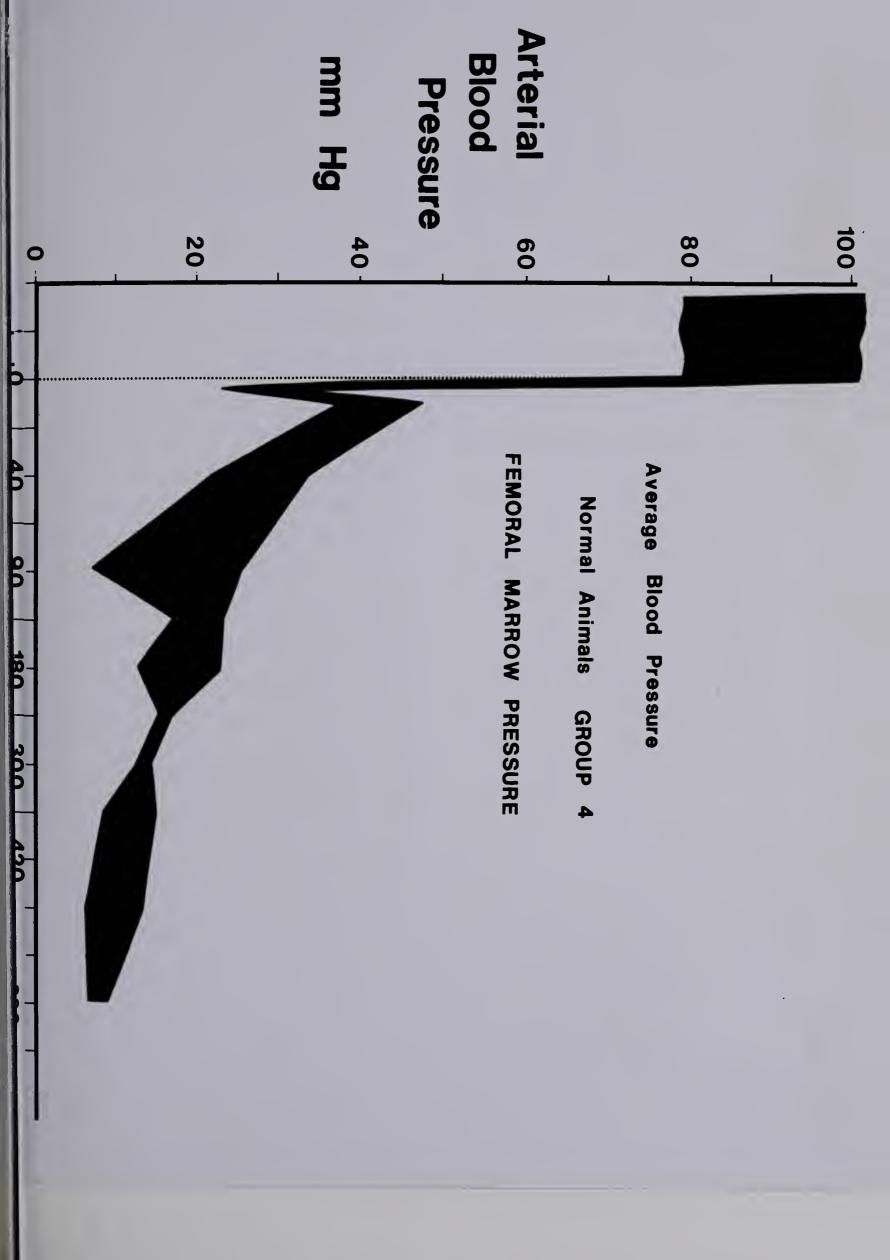
Porto-Caval Shunt Animals

GROUP 5

level which was about three-quarters of the normal level.
(Figure 17) This new pressure was then maintained fair-
ly constantly until the last fifteen to thirty minutes of
life, when a hypertensive episode was frequently observed
in these animals.

A terminal hypertensive period in one or two of our
"normal" dogs subjected to shock was observed. Such epi-
sodes were never as prominent as the ones observed with
the group of porta-caval shunt dogs.

Post-mortem examination of the animals with patent
porto-caval shunts revealed changes similar to those
found in normal dogs with the following exceptions. The
edema of the stomach, duodenum, jejunum and ileum was not
congested or enlarged. There was petechial bleeding from
the stomach mucosa and the upper duodenum but the lower
duodenum, jejunum and ileum were spared from mucosal
slough and hemorrhage. (Figure 18) There was a moderate
amount of intraluminal fluid in the small intestine but
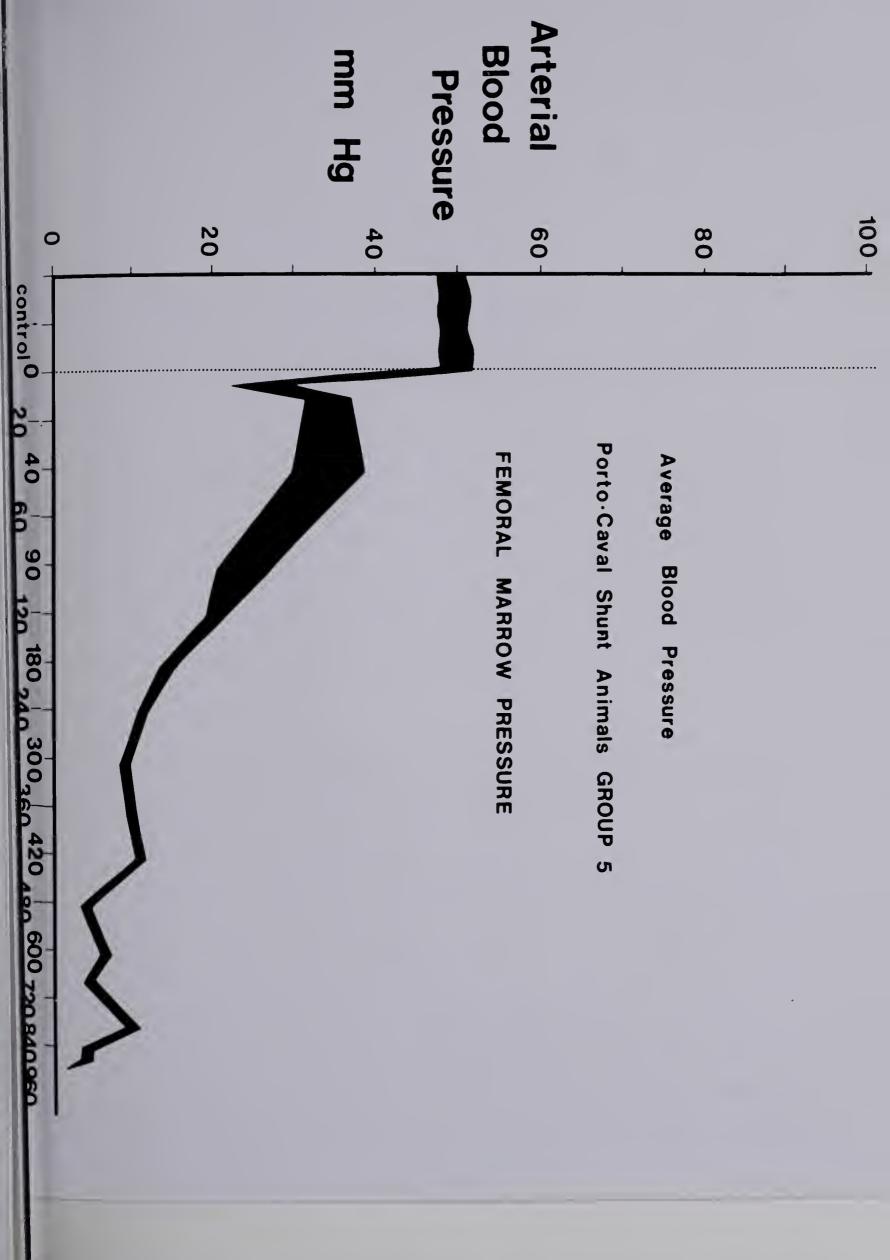large quantities of blood were observed.

Arterial Blood Pressure

mm Hg

Average Blood Pressure

Normal Animals   GROUP 4

FEMORAL MARROW PRESSURE

Femoral Marrow Pressures, Normal and Porto-Caval Shunt Animals

A recording of the blood pressure from the marrow cavity of the right femur was performed in six normal animals during shock. Several of these animals had been cannulated twenty-four to forty-eight hours prior to the production of shock. During this period the pressures recorded from the marrow cavity had remained stable, usually being only slightly lower than the systemic pressure.

In all of the animals there was an immediate drop in the perfusion pressure during shock. (Figure 19) This drop was proportionally greater than the comparable drop in the systemic pressure. There was a marked decrease in the pulse pressure. The marrow pressure did rise again initially, but within the first hour was noted to drop a second time and gradually fell subsequently. There was never a recovery of the pulse pressure during the animal's life.

In addition, it was noted that during the pre-shock period and the early phases of shock, flushing of the femoral catheter with small quantities of saline was met with resistance even though blood could be aspirated

Average Blood Pressure

Porto·Caval Shunt Animals GROUP 5

FEMORAL MARROW PRESSURE

easily. The animal struggled as if in pain and its systemic blood pressure rose while the marrow pressure would fall temporarily to an even lower level.

In the terminal stages of shock, however, it was frequently found easy to infuse much larger quantities of saline (five times as great) with little, if any, resistance, and the animal had no pain response though still conscious. During these terminal phases of shock , occasionally, a negative pressure was recorded in the marrow cavity.

Records of femoral pressure from animals previously prepared with porto-caval shunts demonstrated a some-what different pattern of response. (Figure 20) Initial blood pressure in the marrow cavity tended to be some-what lower in this group (in comparison to the systemic pressure). Instead of an early, rapid drop, there was a gradual downhill tendency, roughly paralleling the drop in systemic pressure. Similar to the picture seen in normal dogs, however, there was a continued decay in pulse pressure and in systolic pressure, with no evidence of stabilization or recovery.

TREATMENT AND ASSESSMENT OF PATHOLOGICAL CHANGES:

Four dogs were then studied in the following manner.
(Group six). With the animals awake and catheters in-
serted, shock was produced. When the animal was in a
terminal condition treatment was commenced. The terminal
clinical course in two animals was the development of
marked hypertension and hyperpnea. In the other two
convulsions occurred. These four animals had been in
shock for an average of seven and three-quarter hours
when therapy was instituted.

The proposal was to administer dibenzylene to pro-
duce vasodilatátion, to attempt to stabilize the blood
pressure temporarily by giving an artificial blood volume
expander, and to rapidly follow the changes in pH which
occurred. Sodium bicarbonate was then to be administered
empirically until the pH should be returned to a physio-
logical range.

It was thus hoped that titration of the peripheral
metabolic acids could be accomplished and an indirect
estimate of their magnitude could be obtained.

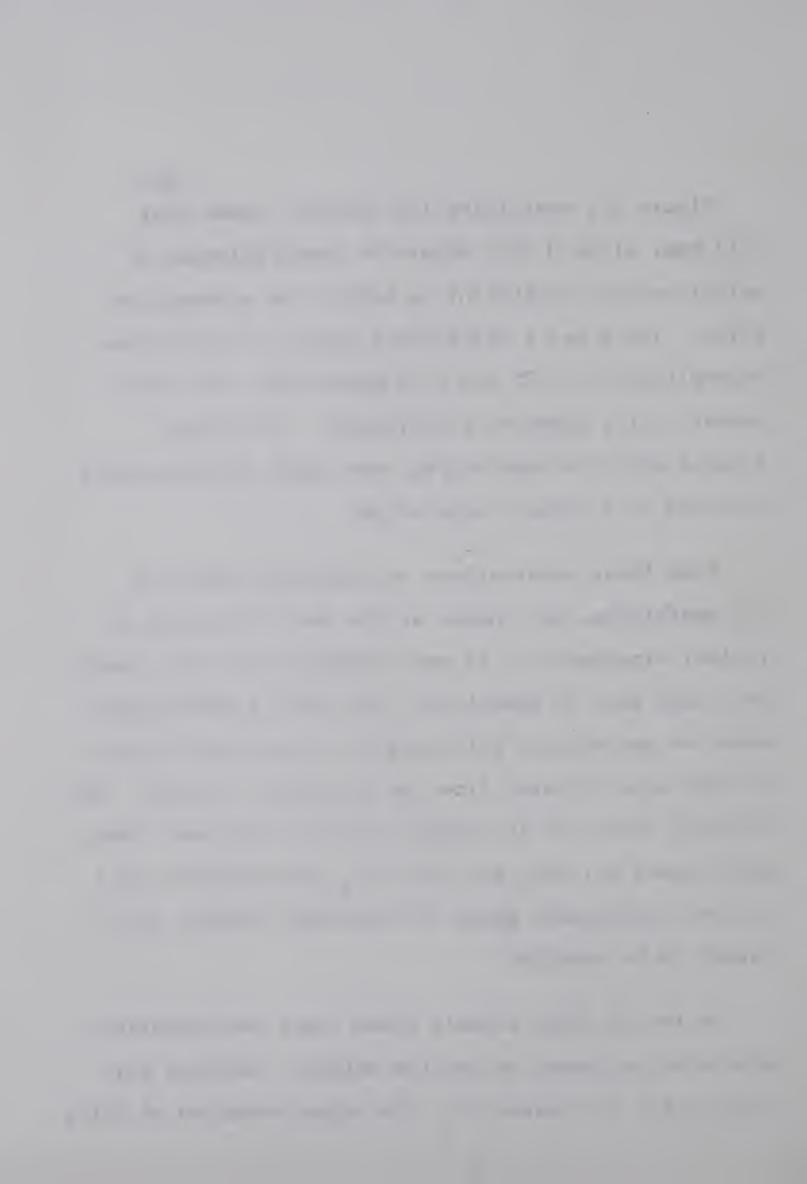| ANIMAL NUMBER:	INITIAL pH	PRETERMINAL pH	IMMEDIATE POST Rx pH	FINAL POST Rx pH	mgm. Sodium Bicarbonate / Min. Shock / Kg.
640	7.44	7.08	6.94	7.10	0.13
933	7.27	7.19	7.15	7.27	0.24
503	7.44	7.27	6.73	6.99	0.25
A-50	7.44 / 16.6	7.43 / 8.1		7.47 / 13.0	0.47

GROUP 6

FIGURE 21

Figure 21, containing the results, shows that
0.13 mgm. of Na H CO$_3$/ minute of shock/kilogram of
weight was not sufficient to buffer the accumulated
acids. There was a significent degree of correction
accomplished by 0.25 and 0.24 mgm/min/kg. but these
amounts still appeared insufficient. The animal
treated with 0.47 mgm/min/kg. was quite satisfactorily
returned to a normal range of pH.

From these observations an arbitrary figure of
0.3 mgm/min/kg. was chosen as the dose to be used in
further experiments. It was considered that this would
be a safe dose to administer, and that it would bring
about an approximate buffering of the metabolic acids
as they were released from the peripheral tissues. The
clinical course of the animal could be observed, then,
with repeat pH, pCO$_2$ and total CO$_2$ determinations and
further bicarbonate given to individual animals as it
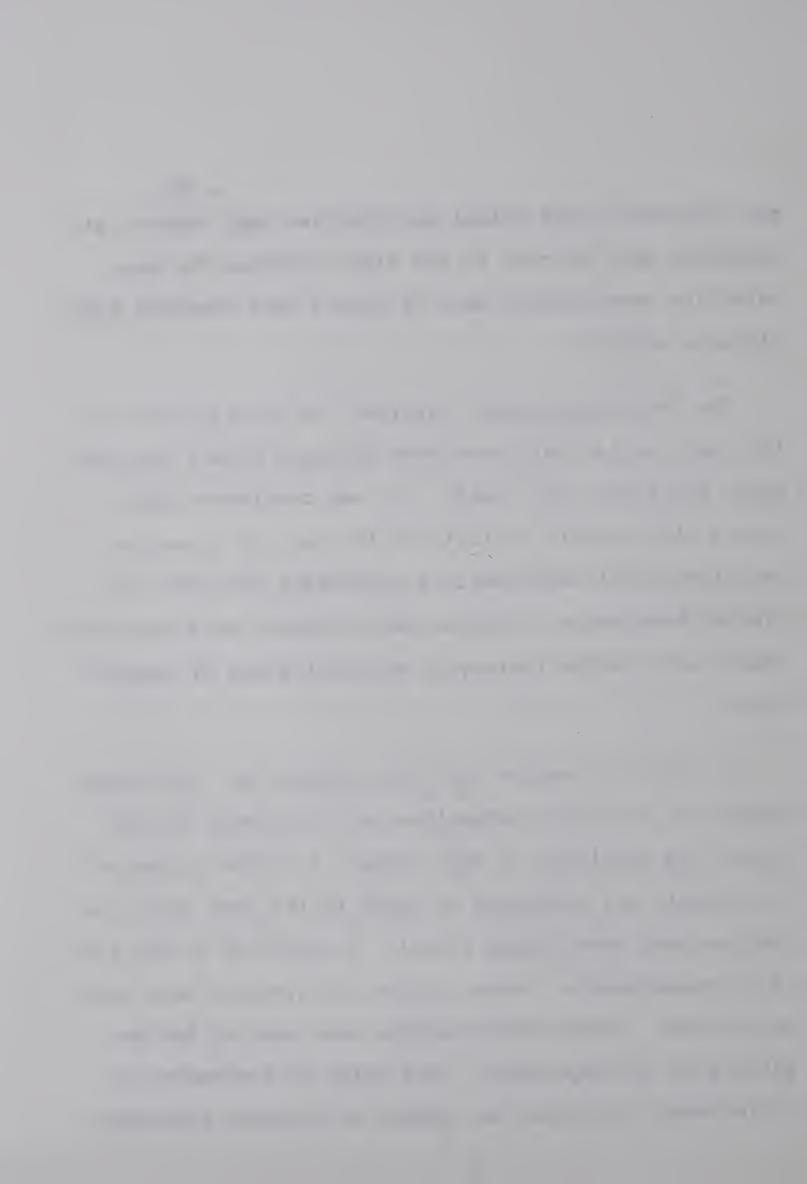seemed to be required.

In two of these animals blood sugar determinations
were also performed during the animals' terminal epi-
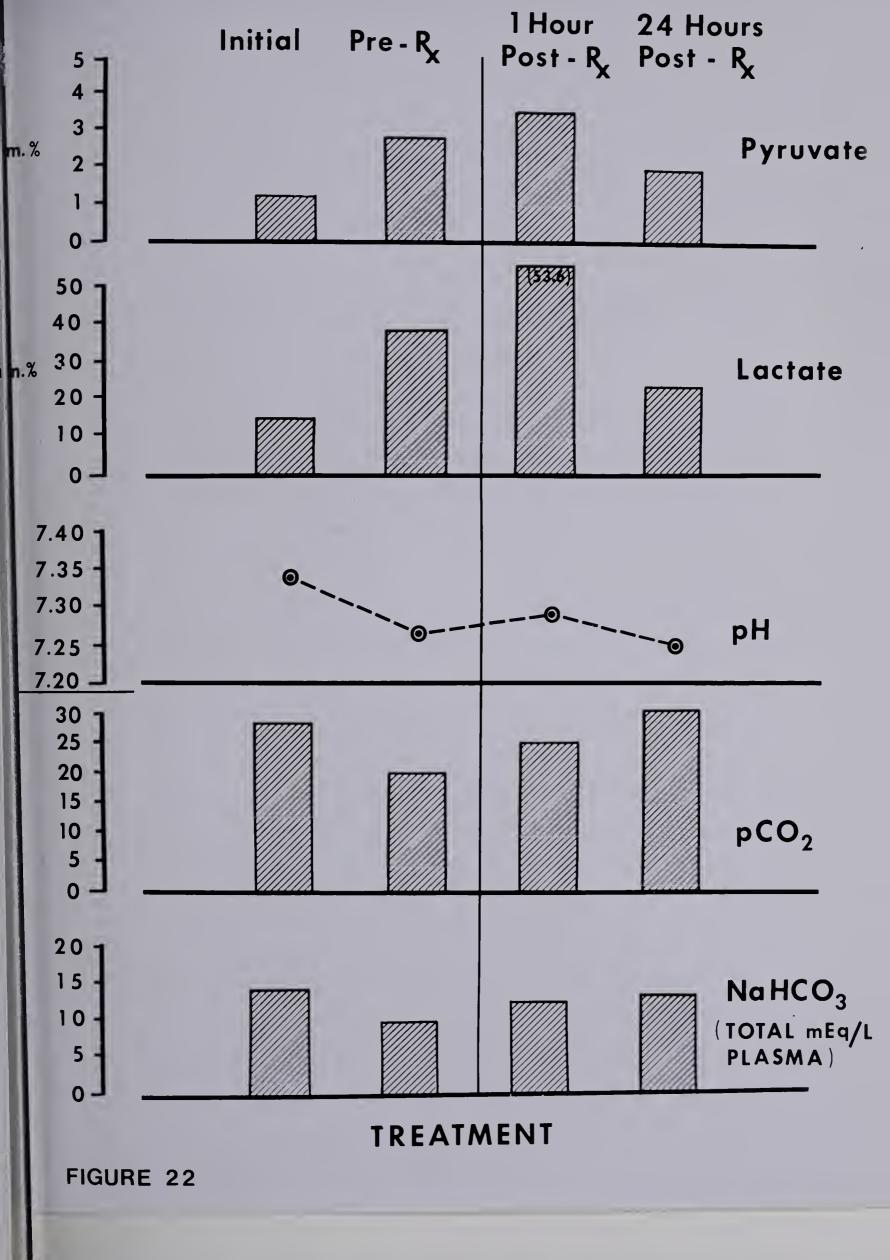sode (prior to treatment). The values obtained of fifty

mgm. percent in one animal and eighteen mgm. percent and
seventeen mgm. percent in the other confirms the more
extensive observations made by others that terminal hypo-
glycemia occurs.

The two animals which survived for several hours in
the above series both developed profound bloody diarrhea
which persisted until death. It was considered that
excess fibrinolytic activity in the face of a denuded
intestinal wall could well be accounting for this con-
tinuing hemorrhage. Epsilon Amino Caproic Acid was added
empirically to the therapy in the next group of experi-
ments.

In order to confirm that the acidosis was developing
because of anaerobic metabolism and to attempt to cal-
culate the magnitude of this change, a further group of
six animals was subjected to shock in the same manner as
the previous ones (Group seven). In addition to the pre-
vious measurements, serum lactate and pyruvate were also
determined. These determinations were made at the be-
ginning of the experiment, just prior to treatment (at
a time when the animal was judged on clinical criterion

FIGURE 22

to be terminally ill), and an hour following the be-
ginning of treatment.

In four of these animals, a further sample was ob-
tained twenty-four hours following the beginning of
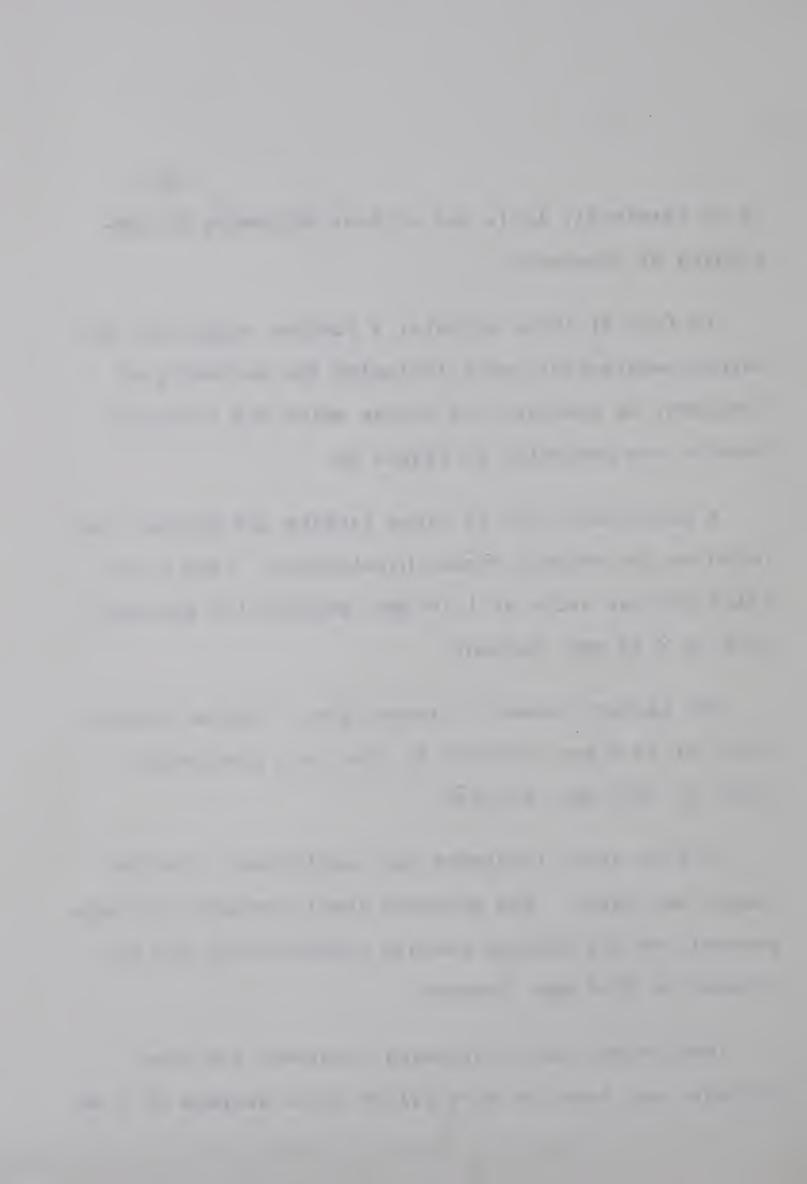treatment to evaluate the change which had occurred.
Results are presented in Figure 22.

A consistent rise in blood lactate and pyruvate was
noted as the animals became hypotensive. From an in-
itial average value of 1.14 mgm. percent the pyruvate
rose to 2.72 mgm. percent.

The lactate showed a larger rise. From an initial
level of 13.8 mgm. percent it rose to a preterminal
value of 38.0 mgm. percent.

An hour after treatment was instituted, a further
sample was taken. The pyruvate level averaged 3.37 mgm.
percent and the average lactate concentration had in-
creased to 53.6 mgm. percent.

Twenty-four hours following treatment the blood
pyruvate was found to have fallen to an average of 1.96

Dog #	Sample Time	Lysis Time
178	1. -24 hrs. prior to shock	Greater than 24 hours
178	2. -2 hrs. of shock, immediately prior to treatment	- 6 minutes
178	3. -1 hour following treatment	3 1/2 hours
9	1. Immediately prior to shock	- 4 hours
9	2. -1 hour post treatment	Greater than 12 hours
9	3. -21 hours post treatment	- 7 hours-20 minutes
47	1. Prior to shock	- 1 1/2 hours
47	2. Prior to treatment 3 1/2 hours of shock	Sample lyses immediately on clotting

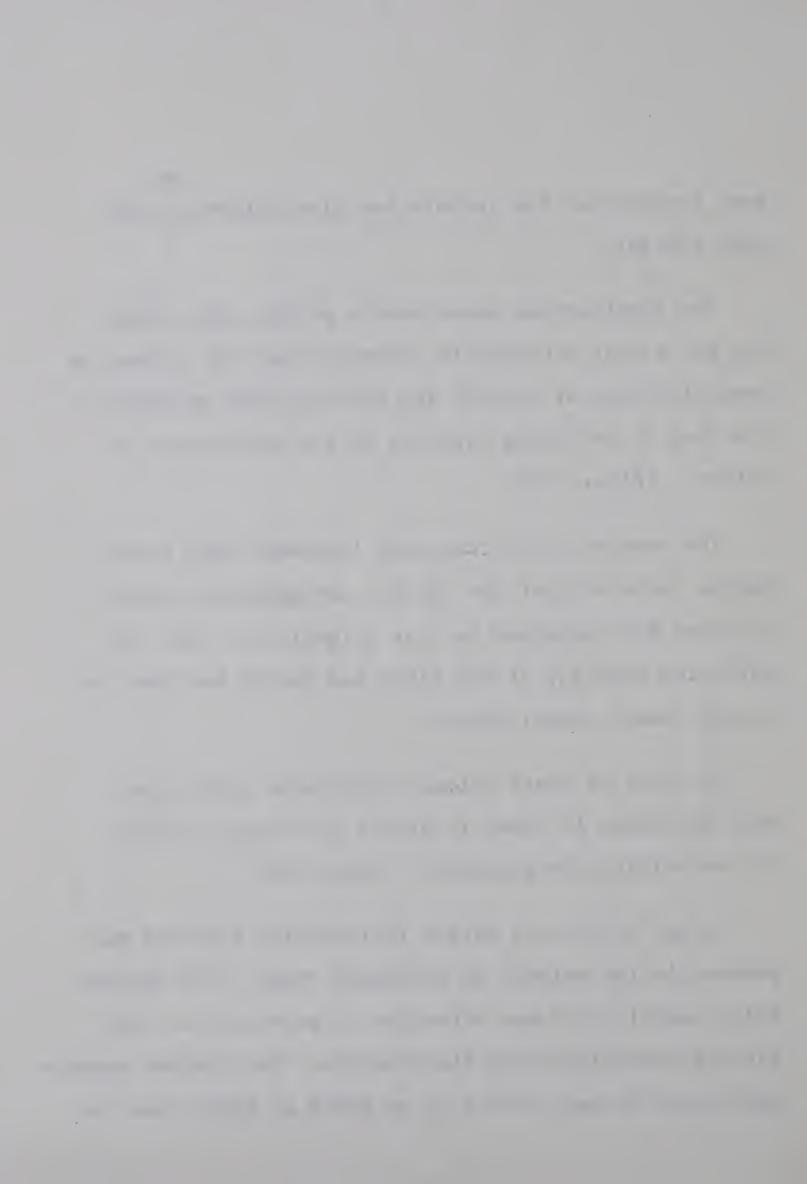Figure 23 . Euglobulin Lysis Time, Group VII

mgm. percent and the lactate had also fallen to 22.4
mgm. percent.

The simultaneous measurements of pH, pCO_2, total
CO_2 and actual bicarbonate revealed that the increasing
concentrations of lactate and pyruvate were mirrored in
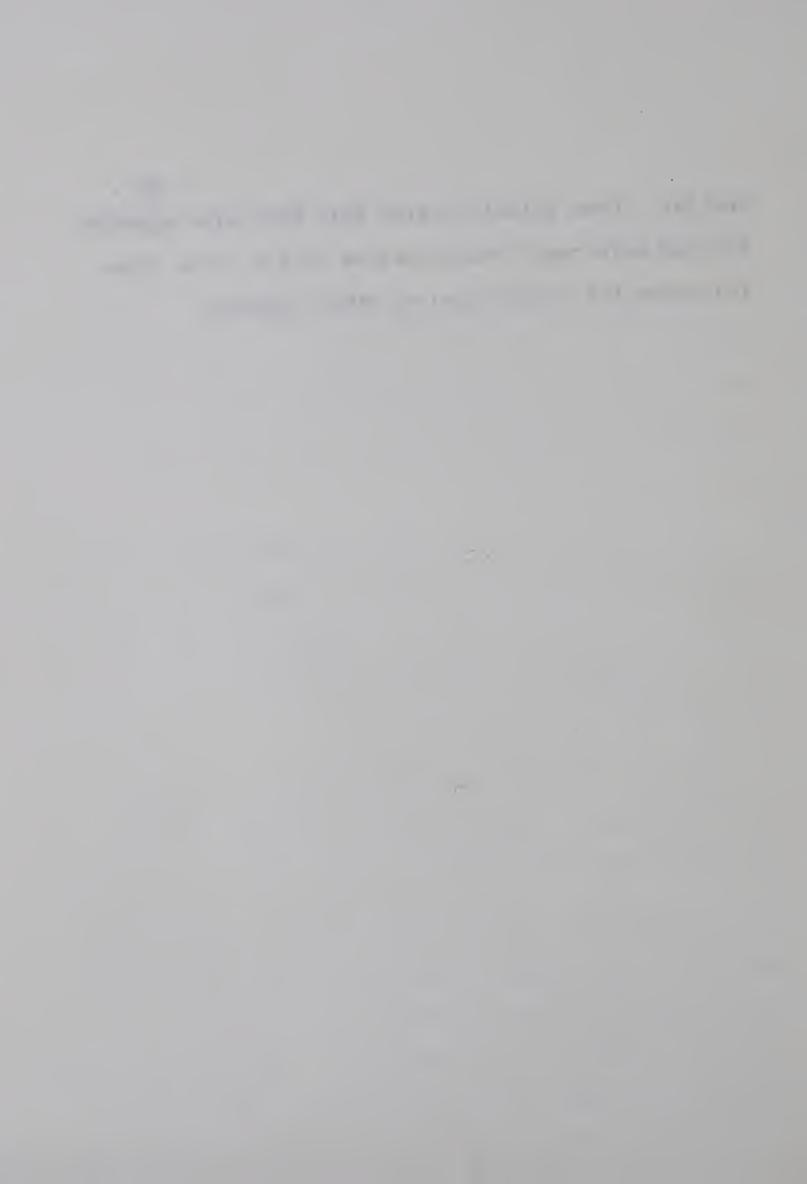the drop in buffering capacity of the bicarbonate re-
serves. (Figure 22).

The samples taken following treatment with bicar-
bonate revealed that the lactate and pyruvate concen-
trations had continued to rise slightly but that the
buffering capacity of the blood and the pH had been re-
turned toward normal values.

In three of these animals euglobulin lysis times
were performed in order to assess the effect of EACA
in controlling fibrinolysis. (Figure 23)

As can be seen, a marked fibrinolytic activity was
present in the animals in prolonged shock. The Epsilon
Amino Caproic Acid was effective in partially or com-
pletely controlling the fibrinolysis. The treated animals
were noted to have little or no blood in their stool or

vomitus. Each animal treated with EACA also appeared to show more rapid stabilization of its vital signs following the institution of other therapy.
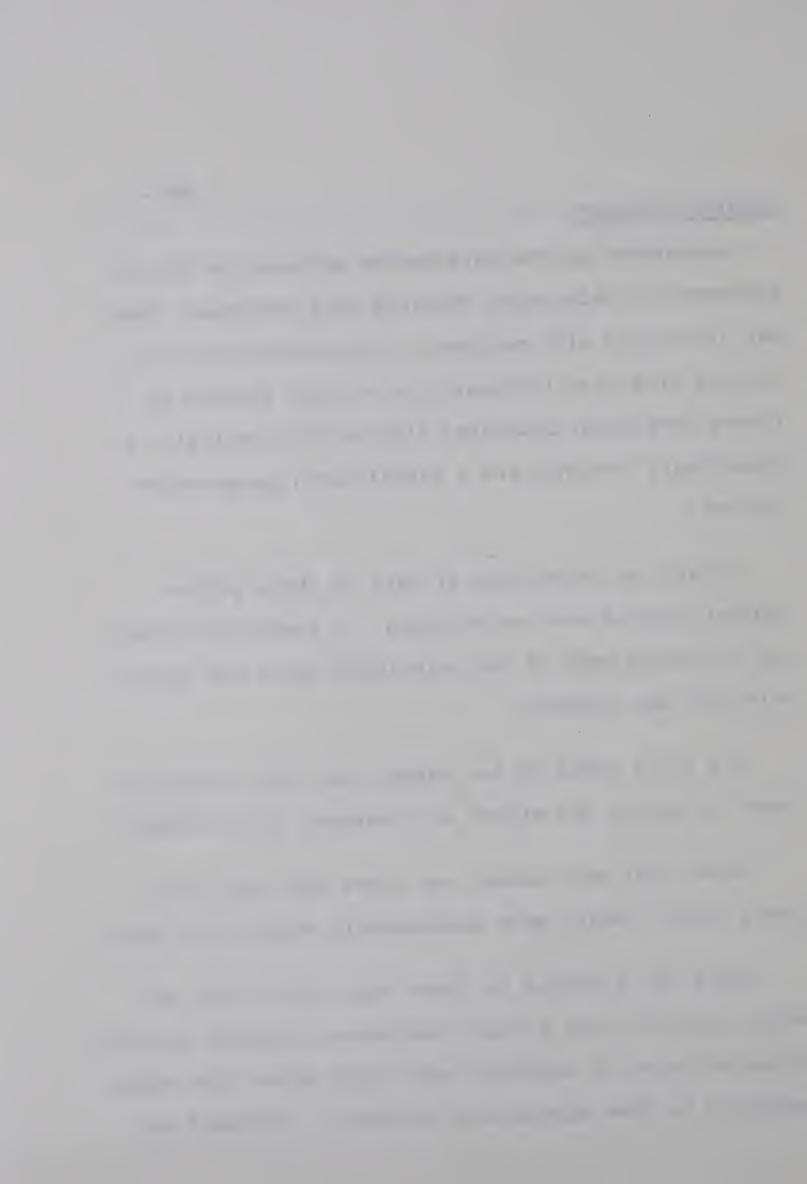
COMBINED THERAPY

Assessment of the information gathered by the experiments to this point revealed that prolonged shock was associated with peripheral vasoconstriction, decreased effective intravascular volume, slowing of tissue perfusion, increased fibrinolytic activity, a hemorrhagic tendency and a significant, progressive acidosis.

Results of correction of each of these pathological changes were encouraging. A combination therapy embodying each of the principles which had proven effective was adopted.

The final group of ten animals was then studied in order to assess the effect of treatment (Group eight).

Seven dogs were normal and three dogs had portocaval shunts (which were subsequently shown to be open).

Shock was produced in these dogs and the BP, pH, pCO_2, total CO_2 and actual bicarbonate followed serially. Repeated doses of endotoxin were given where the animal appeared to show spontaneous recovery. Treatment was
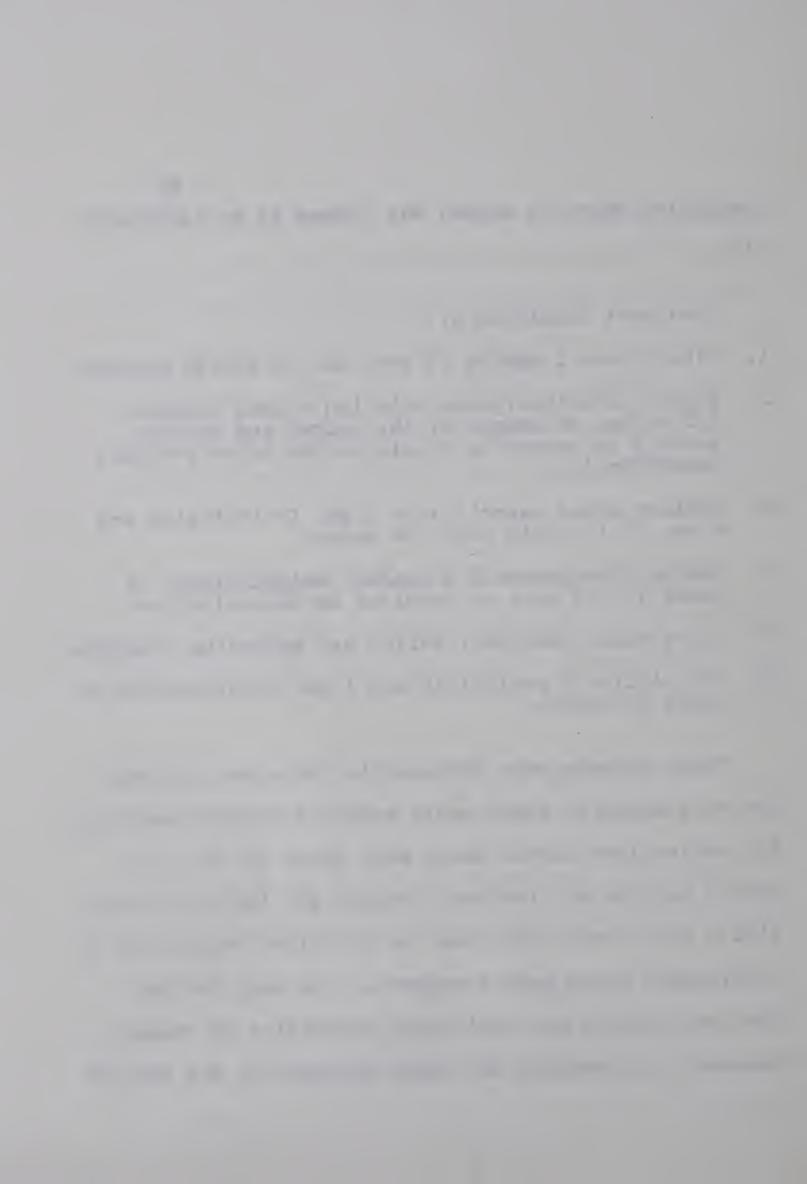
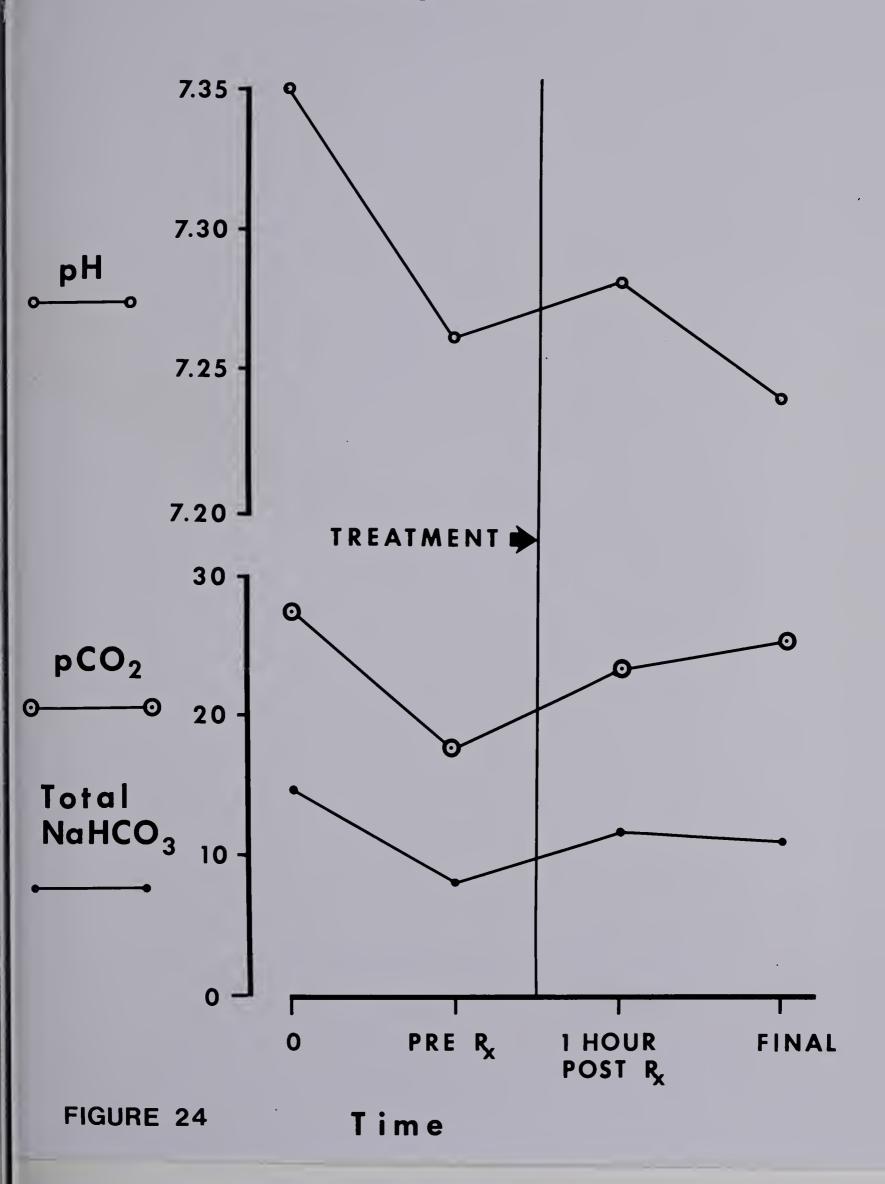instituted when the animal was judged to be terminally
ill.

Treatment consisted of:

1. Dibenzylene 1 mgm/kg IV over ten to thirty minutes;

2. Bovine albunine-Tyrode solution volume expander
   1.5 cc/kg. of weight of the animal and further
   amounts as needed to stabilize the blood pressure
   (ave=200cc);

3. Epsilon amino caproic acid 1 gm. Iv initially and
   4 gm. IV in fluid every 24 hours;

4. Sodium bicarbonate 0.3 mgm/kg. weight/minute of
   shock IV and more as required on re-evaluation;

5. Intravenous dextrose, saline and potassium chloride;

6. One million U penicillin and 1 gm. chloromycetin IV
   every 12 hours.

These animals were observed in the state of shock
for an average of eight hours before treatment was begun.
All medications listed above were given in the first
thirty minutes of treatment, except for the intravenous
fluids which were continued for the first thirty-six to
forty-eight hours post-treatment. The only further
therapy required was additional quantities of volume
expander to stabilize the blood pressure in the face of

Average Values:

FIGURE 24

Time

Time in Shock	Dog #	Survival Time	Cause of Death	Antibiotic Stopped
6 1/3 hrs.	959	5days-2hrs.	Overwhelming Infection	48 hrs.
3 1/2 hrs.	957	20days-4hrs.	Metastatic Deposits of Infection	1 week
13 hrs.	72	13 hrs.	Hypovolemia	13 hrs.
4 1/4 hrs.	138	3 1/2 hrs.	Hypovolemia	3 1/2 hrs.
6 hrs.	139	11 3/4 hrs.	Continued Hemorrhage from intestine operative wound	11 hrs.
1 1/2 hrs.	178	24 3/4 hrs.	Hypovolemia (Dog had diarrhea prior to shock)	24 hrs.

Figure 25   Cause of Death In Treated Animals

Time in Shock	Dog #	Survival Time	Cause of Death	Antibiotic Stopped
3 1/2 hrs.	47	24 1/2 hrs.	Vomited, aspirated and died of immediate asphyxia	24 hrs.
10 3/4 hrs.	965	4 1/4 hrs	Cardiac Failure	4 1/4 hrs.
4 hrs.	9	22 days	Metastatic Foci of Infection	1 week
25 1/2 hrs.	79	3 1/2 days	Diffuse overwhelming Pneumonia	36 hrs.

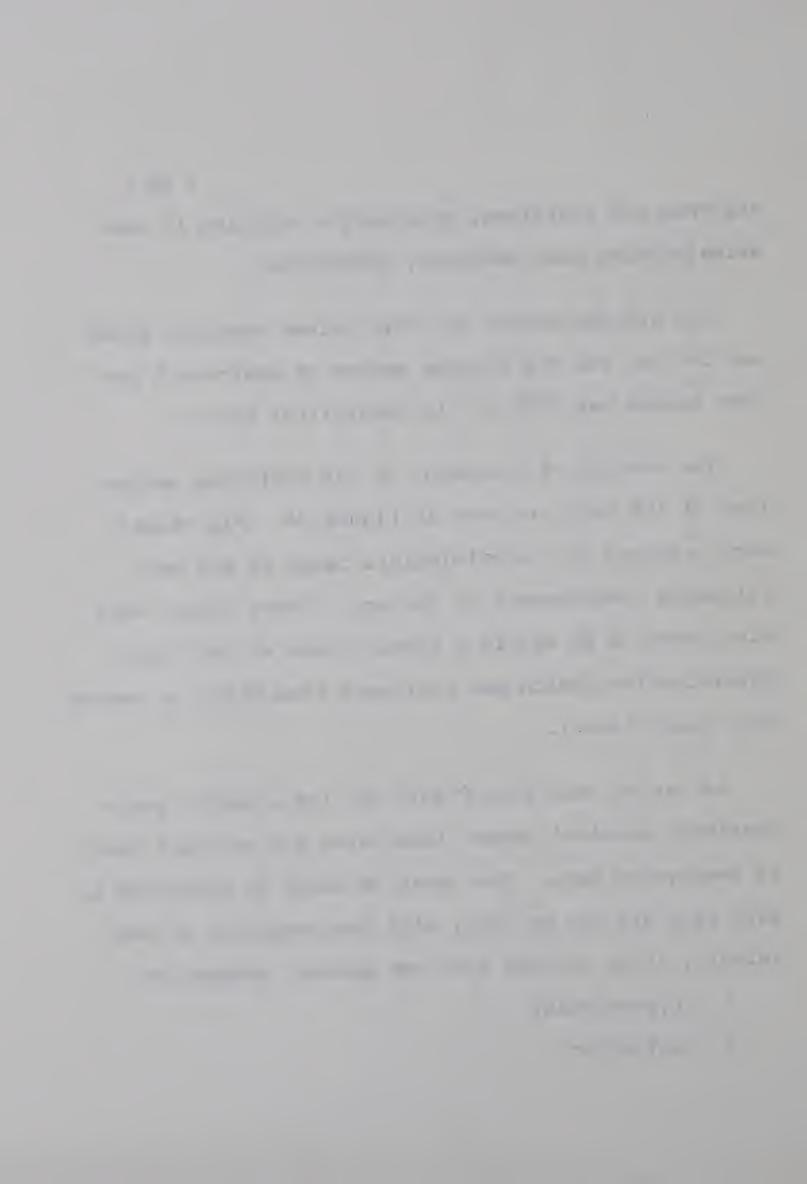Figure 25   Cause of Death In Treated Animals

diarrhea and additional electrolyte solution in some
animals which were obviously dehydrated.

The average amount of extra volume expander given
was 200 cc. and the average amount of Dextrose 5 per
cent saline was 2000 cc. in twenty-four hours.

The results of treatment on the buffering mechan-
isms of the body are seen in Figure 24. All values
were returned to a physiological range by one hour
following commencement of therapy. These values were
also found to be within a normal range at the final
determination (which was performed from eight to twenty-
four hours later).

As can be seen from Figure 25, the animals' post-
treatment survival ranged from three and one-half hours
to twenty-two days. The cause of death is presented in
each case and can be seen, with the exception of two
animals, to be divided into two general categories;

1. hypovolemia;

2. infection.

Early deaths were directly related to insufficient
volume replacement. Central venous pressure, which was
being monitored periodically in these animals, was con-
sistently low (except for dog number 965). In dog
number 965, the bicarbonate solution was administered
through a catheter lying close to the right atrium.
At autopsy the myocardium was dilated, flabby in con-
sistency, and had multiple petechial hemorrhages
throughout the muscle suggesting that direct endo-
thelial damage had been produced. In addition, the
central venous pressure was elevated in this animal.
Following this observation the bicarbonate was always
given in a distal vein or intra-arterially.

One animal died from asphyxia, (from aspiration of
vomitus) and the remaining animals all developed
severe, diffuse infections in the post-treatment period.
Microscopic examination of the tissues from the animals
which died several days following shock, showed the
macrophages of the liver and lung to be filled with
particulate matter suggesting a massive engorgement of
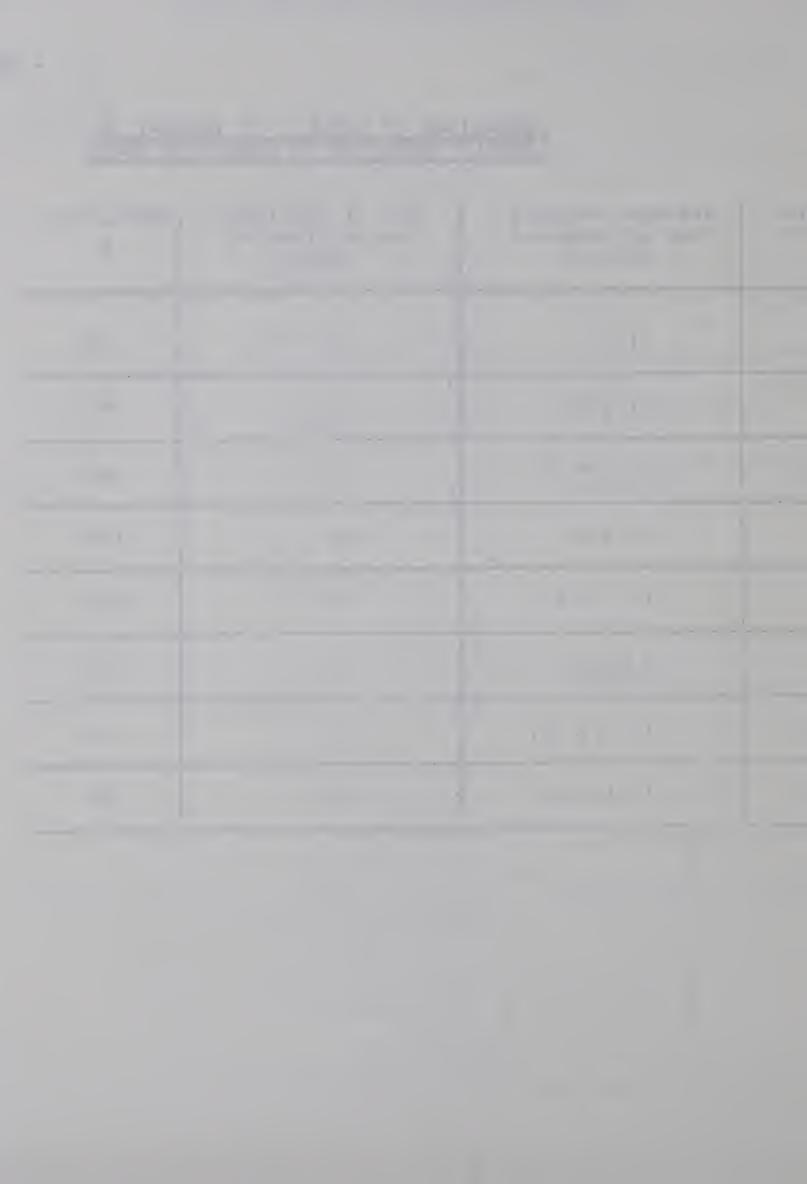the reticulo-endothelial system.

COMPARISON OF RESULTS OF THERAPY IN ANIMALS SUBJECTED TO ENDOTOXIN SHOCK

Group Number	No. of Animals	Aver. Dose of Endotoxin	Treatment	Aver. Length of Time in Shock Prior to Treatment
e	6	5 mgm/kg	Heparin 2 mgm/kg Nembutal 30 mgm/kg	0
o	6	5 mgm/kg	Heparin 2 mgm/kg Nembutal 30 mgm/kg	0
ree	16	5 mgm/kg	Heparin 2 mgm/kg Nembutal 30 mgm/kg	0
ir	16	9 mgm/kg	Heparin 2 mgm/kg	0
ve	7	11 mgm/kg	Heparin 2 mgm/kg Porto-Caval Shunt	0
	4	12 mgm/kg	Heparin 2 mgm/kg Dibenzyline 1 mg/kg Plasma Expander 15 cc/kg Sodium Bicarbonate 0.27 meq/kg/min. Glucose Antibiotics	7 3/4 hr.
en	6	10 mgm/kg	Heparin 2 mgm/kg Dibenzyline 1 mgm/kg Plasma Expander 15 cc/kg Sodium Bicarbonate 0.33 meq/kg/min. Glucose Antibiotics EACA 4 gm/24 hr. I.V.	4 hr.
ht	10	12.5 mm/kg	Heparin 2 mgm/kg Dibenzyline 1 mgm/kg Plasma Expander 15 cc/kg Sodium Bicarbonate 0.33 meq/kg/min. Glucose Antibiotics EACA 4 gm/24 hr. I.V.	8 hr.

COMPARISON OF RESULTS OF THERAPY IN
ANIMALS SUBJECTED TO ENDOTOXIN SHOCK

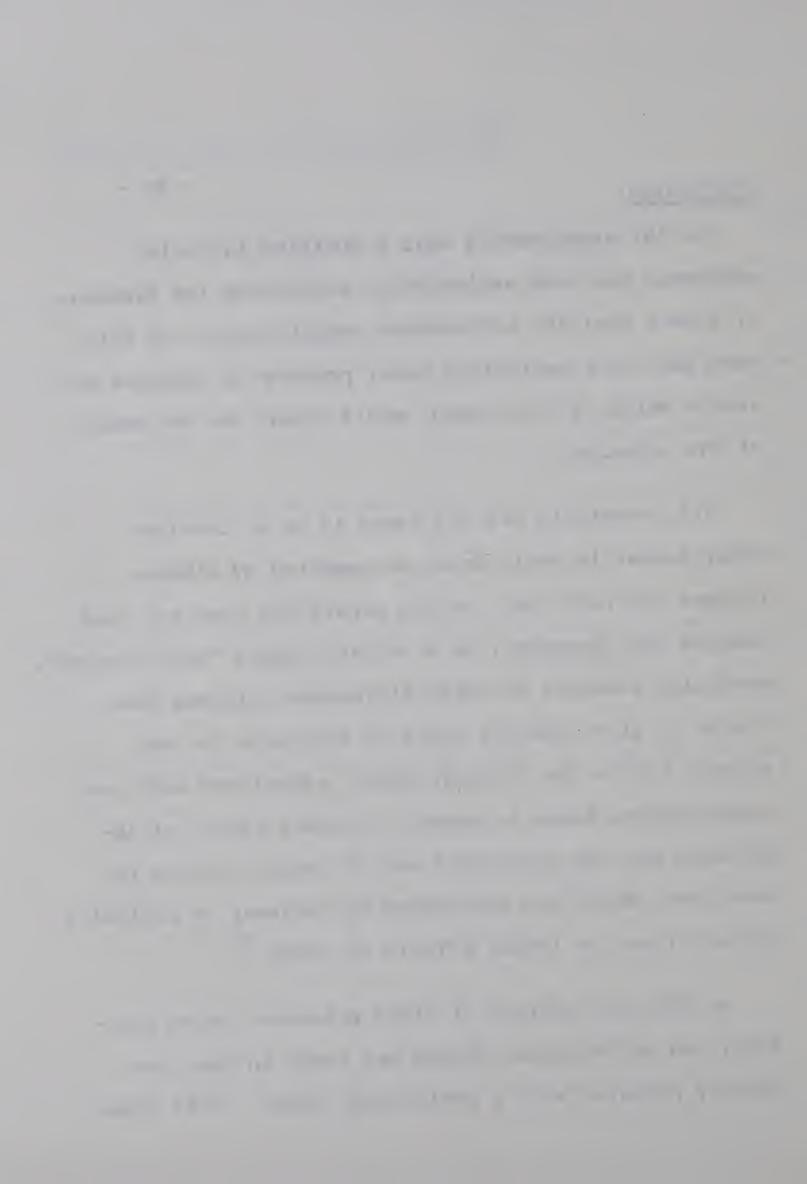| Group Number	Average Survival Time of Deceased Animals	No. of Survivors Greater than 48 Hours	Mortality %
One	11 hr.	3	50
Two	11 ½ hr.	2	67
Three	17 3/4 hr.	3	81
Four	10 ½ hr.	0	100
Five	10 1/7 hr.	0	100
Six	3 ½ hr.	0	100
Seven	19 2/3 hr.	3	50
Eight	13 1/3 hr.	4	60

DISCUSSION:

In the experimental work a purified bacterial endotoxin was used exclusively, confirming the findings of others that the intravenous administration of this material, in a sufficient dose, produces a sequence of events which, if prolonged, would result in the demise of the organism.

This endotoxin was not found to be as consistently lethal in small doses as reported by others. Perhaps the fact that the dog population used was cold adapted and therefore, to a certain degree "pre-stressed", partially accounts for this difference. It was necessary to give repeated doses of endotoxin to some animals before the clinical signs, associated with decompensation, began to appear. Another factor of importance was the consistent use of Heparin during the experiment which has been shown by Hardeway to partially protect from the lethal effects of shock.[63]

A different pattern of blood pressure, pulse pressure, and pathological change was found in dogs previously prepared with a porto-caval shunt. This shows
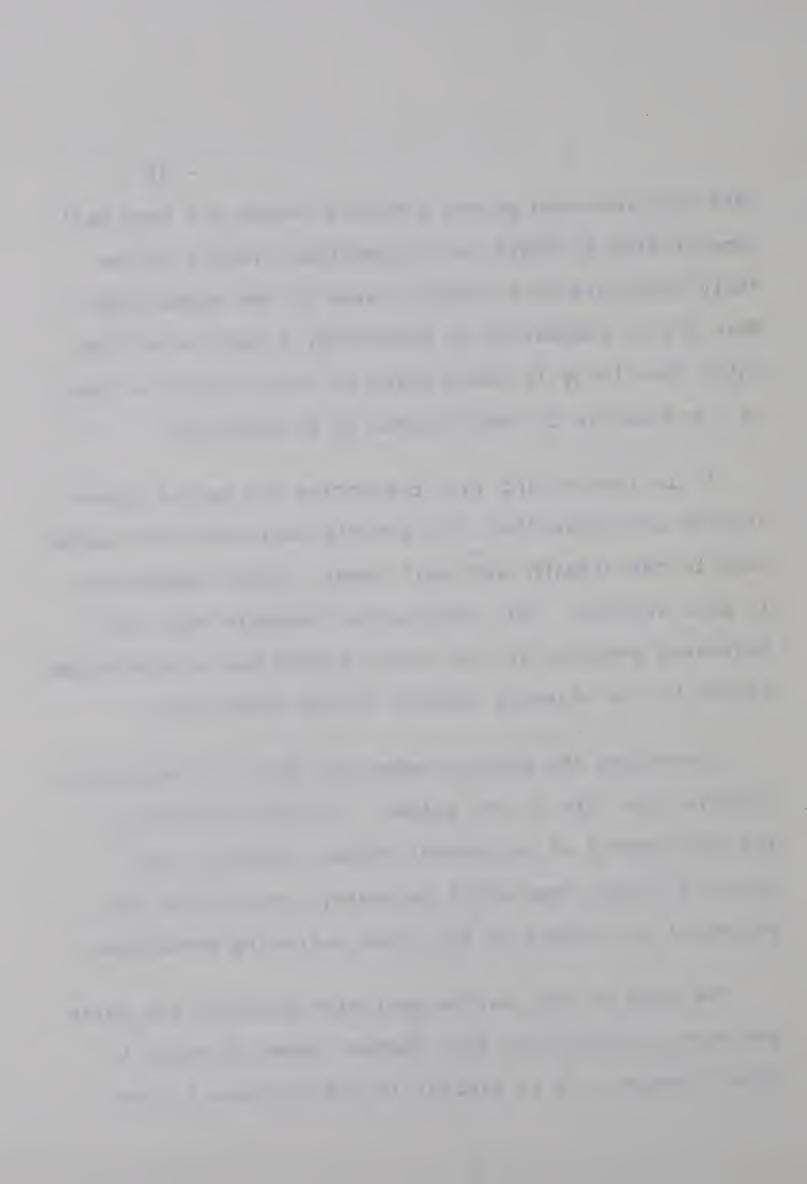
that the increased portal pressure (which has been well
demonstrated in dogs) is a significant factor in the
early blood pressure changes noted in the normal dog.
When portal congestion is prevented, a pattern of vas-
cular reactivity is found which is very similar to that
of a man who is in shock caused by an endotoxin.

It is interesting that preventing the portal hyper-
tension and congestion also greatly decreases the changes
seen in the stomach and small bowel. Liver congestion
is also avoided. This observation suggests that the
increased pressure in the venous system has a deleterious
effect in the visceral tissues of the normal dog.

Preventing the portal congestion does not materially
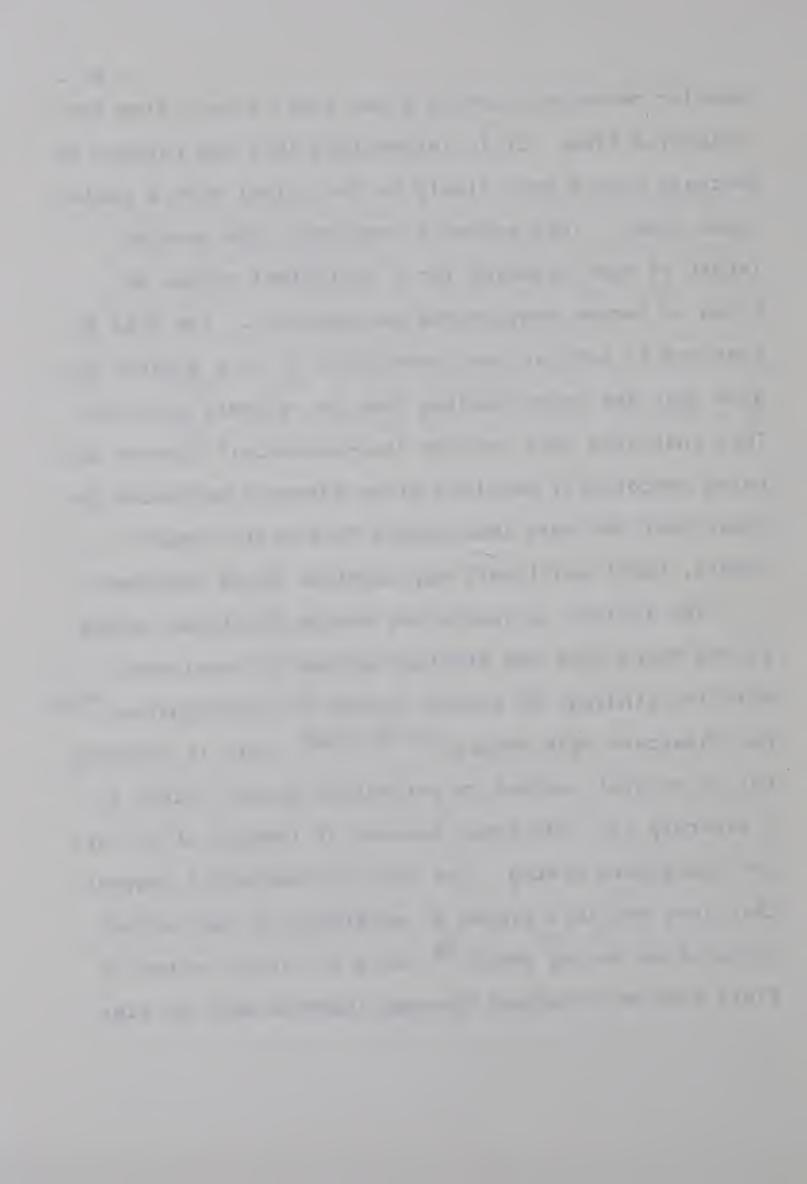lengthen the life of the animal. It does not prevent
the development of peripheral edema, cyanosis, poor
tissue filling, hematocrit increase, conjunctival en-
gorgement or changes in the blood buffering mechanisms.

The drop in bone marrow perfusion pressure and pulse
pressure is consistent with changes shown to occur in
other tissues. It is similar to the decrease in the

superior mesenteric artery flow, renal artery flow and peripheral flow. It is interesting that the pattern of decrease occurs more slowly in the animal with a porto-caval shunt. This probably represents the greater length of time required for a sufficient volume of blood to become sequestered peripherally. The fall in pressure is constant and eventually is to a greater de-gree than the corresponding drop in systemic pressure. This indicates that various "non-essential" tissues are being temporarily deprived of an adequate perfusion in order that the more immediately "critical" organs (brain, heart and liver) may continue to be perfused.

The failure to record any change in plasma volume by the Evans blue dye dilution method is consistent with the findings of several groups of investigators,[75,81] but disagrees with others.[19,78,79,80] This is probably not an accurate method of estimating plasma volume in a severely ill individual because of leakage of the dye and inadequate mixing. The rise in hematocrit suggests that less and less plasma is available to the central circulation during shock.[78] Also the large volume of fluid lost by an animal through diarrhea must be sig-

nificantly depleting the extra cellular water and electro-
lyte stores.

The slight change noted in pH has been recorded by
others, but the degree of this change and the alterations
in buffering capacity of the blood as demonstrated by
the drop in serum bicarbonate have never been emphasized.
84,85 The magnitude of this change was, in addition,
indirectly demonstrated. The study suggested that an
amount of bicarbonate equal to 0.3 mgm/kgm. wt/minute
of shock was an amount sufficient to buffer the shocked
animal and bring his pH and total bicarbonate back to a
physiologically acceptable range. Subsequent experiments
on resuscitation confirmed this as being a good approx-
imation of the rate at which acidosis developed.

From the work of Ledingham and Norman, it is observed
that an animal in complete circulatory arrest develops
acidosis at the rate of 1.1 meq./kg/min. (123 mgm. of
bicarbonate kg/min).[130] By comparison with results, of
the foregoing experiments it could be estimated that
approximately 1/300 to 1/400 of the animal's body weight

can be considered to be completely deprived of oxygen

from the onset of hypotension, judging by the rate of

development of acidosis.

That this acidosis is derived from the products of

anerobic metabolism is confirmed by the demonstration

that there is a gradual increase in the concentration

of lactate and pyruvate. That they continue to rise

following the beginning of treatment suggests that the

acidotic metabolites were produced in the peripheral

tissues and were "piled up" there because the circula-

tion was inadequate to return them to the "central"

circulation.

It can be seen that opening the peripheral circula-

tion by the administration of an adrenergic blocking

agent could lead to an adverse effect on the heart, un-

less this degree of acidosis were corrected by the

simultaneous administration of bicarbonate.

The results of the "treated" group of animals de-

monstrates that is is possible to resuscitate severely

"shocked" animals and that many of the physiological

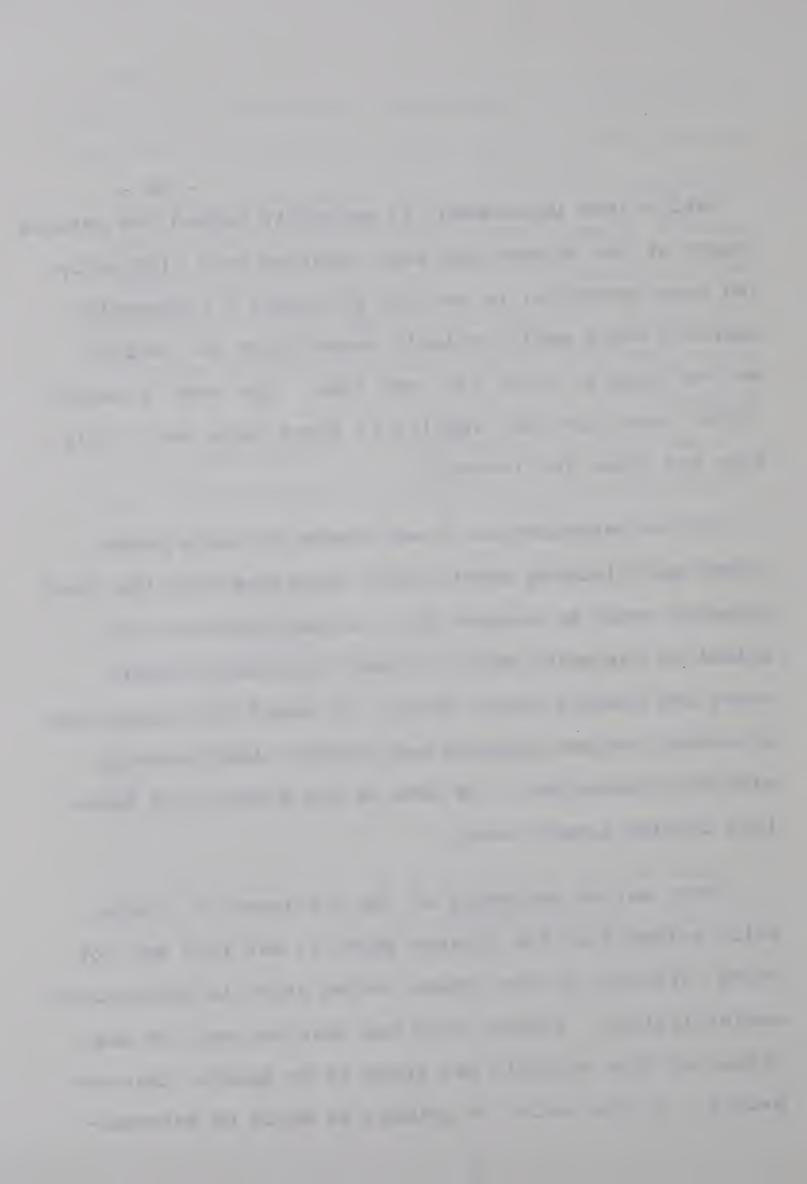changes which have been observed can be corrected.

The fact that peripheral vasoconstriction is present has been recorded in different ways by other investigators.[19,38,133] In addition, others, on the basis of clinical observations, have arrived at the same conclusion.[51,131,132] The low central venous pressure in endotoxic shock which mirrors a decreased venous return has been verified by several research groups.[33,40]

Controversy in the field of therapy has arisen as to the most rational approach to improving the venous return to the heart and to reversing the tendency of blood to be sequestered peripherally. Many reports have centered on the use of vasoconstrictors, the "squeeze it out" policy.[57,60,133,134,135] Others have dealt with the use of volume dilutional therapy, (the "sweep it out" approach), the most effective of which appears to be low molecular weight dextran.[120] Still a third group of workers has advocated and presented evidence to favor the use of vasodilators or adrenergic blocking agents, the "let it out" theory.[19,59,131,132,136,137]

While some improvement in mortality beyond the natural
course of the disease has been reported both clinically
and experimentally, no one has presented a therapeutic
approach which would reliably resuscitate the patient
who had been in shock for some time. The term "irrever-
sible" shock has been applied to these cases and little
hope was shown for recovery.

In the experiments, it was chosen to use a potent
adrenergic blocking agent, fully realizing that the blood
pressure could be dropped in an already severely ill
animal to the point where coronary circulation would
cease and cardiac arrest occur. To avoid this occurrence,
an osmotic volume expander was infused simultaneously
with the dibenzylene. In none of the animals did immed-
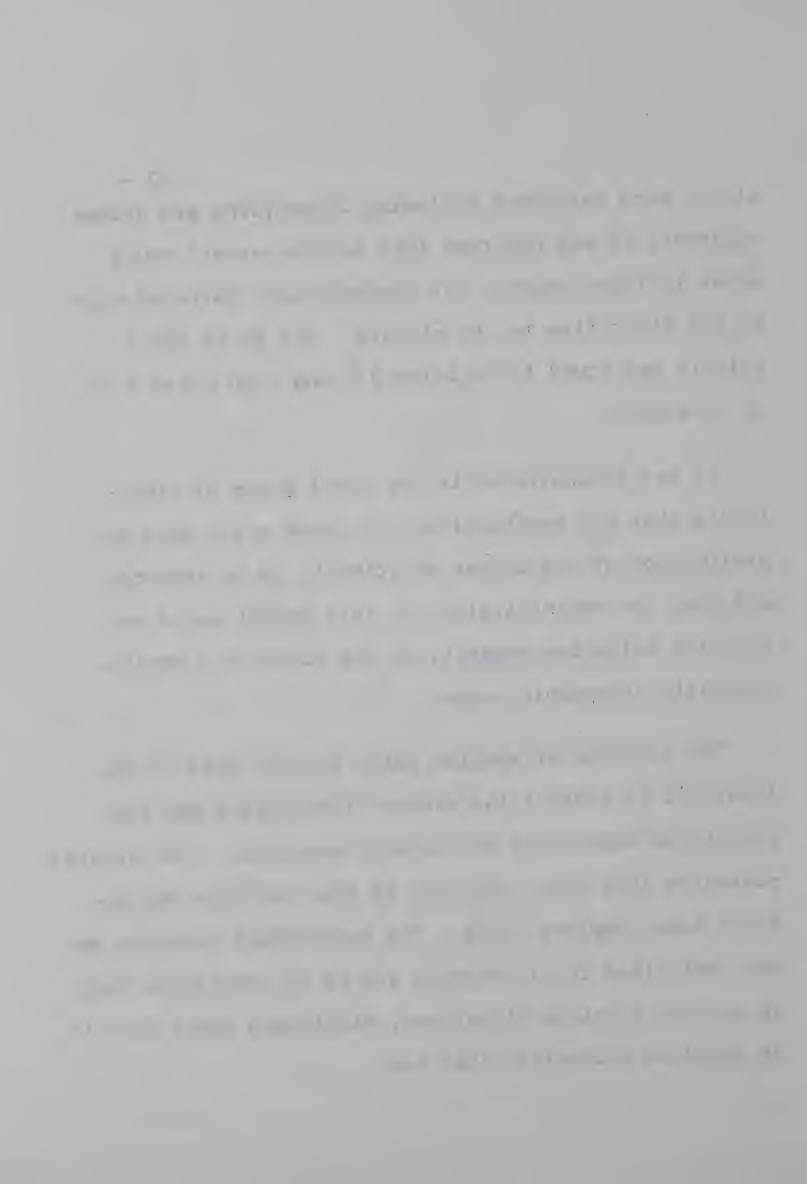iate cardiac arrest occur.

There was an awareness of the existence of a meta-
bolic acidosis in the tissues which it was felt was not
being reflected in the venous system prior to dibenzylene
administration. Indeed, this was observed and the mag-
nitude of this acidosis was found to be greater than ex-
pected. In the series of animals in which pH determin-

ations were performed following dibenzylene and volume expander, it was observed that cardiac arrest would occur in those animals not appropriately buffered within the first five to ten minutes. The pH in these animals was found to be below 6.9 and even below 6.75 on occasions.

It was demonstrated in the final group of experiments that 0.3 mgm/kg/minute of shock was a good approximation of the degree of acidosis to be expected and that the administration of this amount would return the buffering capacity of the blood to a physiologically acceptable range.

The addition of epsilon amino caproic acid to the treatment to control the excess fibrinolysis and the associated hemorrhage was largely empirical. The studies presented lend some rationale to this addition but deserve more complete study. The hemorrhagic tendency was not controlled in all animals and it is considered that, in certain clinical situations, fibrinogen might have to be added to accomplish this end.

Early deaths were usually seen in animals who continued to bleed or to have severe diarrhea. A blood transfusion was not given to any animal, but it was considered that transfusion would probably have materially improved the animal's chance of survival.

The administration of large quantities of glucose-containing fluids and electrolyte solution are essential. It is only necessary to consider the depletion of glucose stores which have been demonstrated by others and the diarrhea, vomiting, hyperpnea, lacrimation and salivation which are consistently observed in these animals to understand this need.

Antibiotics to protect the severely stressed animal were administered initially because other research investigators have found them necessary during the recovery phase.[19] As a result of the foregoing experiments it appears that the animals' cellular and humoral defense mechanisms are markedly depressed, and that antibiotic therapy would rationally be employed for periods longer than one week following shock.
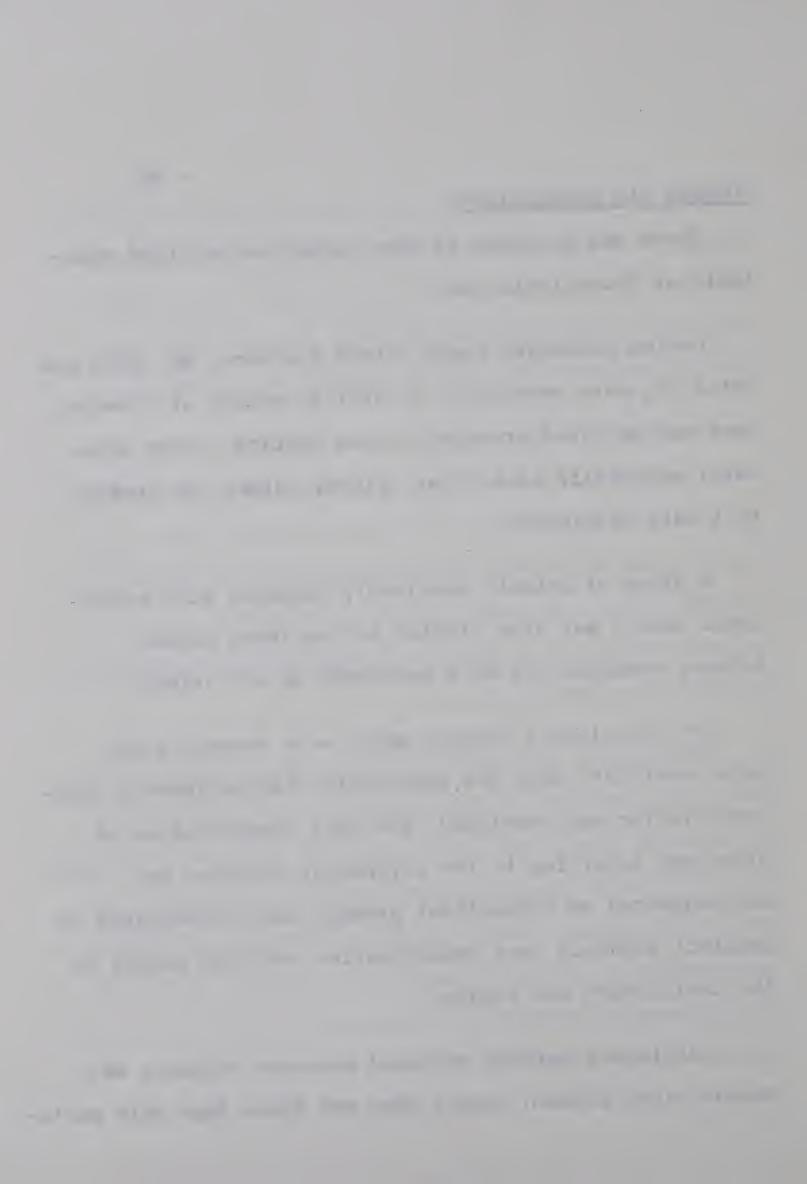
SUMMARY AND CONCLUSIONS:

Shock was produced in dogs using the purified endo-
toxin of Escherichia coli.

During prolonged shock, blood pressure, pH, pCO_2 and
total CO_2 were measured. In similar groups of animals,
bone marrow blood pressure, serum lactate, serum pyru-
vate, euglobulin lysis time, plasma volume and hemato-
crit were determined.

A group of animals previously prepared with porto-
caval shunts was also studied in the above manner.
Autopsy examinations were performed on all animals.

The circulatory changes which were demonstrated
were consistent with the hypothesis that peripheral vaso-
constriction had developed, and that sequestration of
blood was occurring in the peripheral vascular bed. It
was suggested on theoretical grounds and corroberated by
indirect evidence that sequestration occurred mainly in
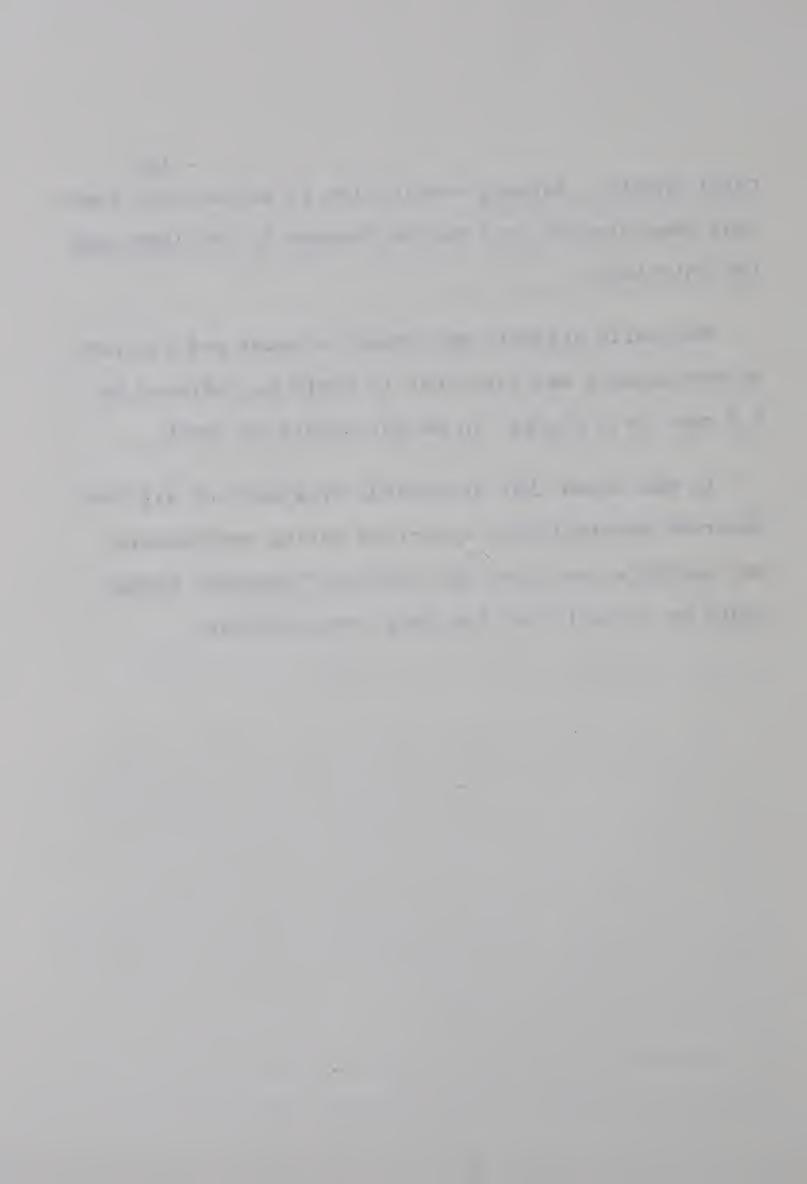the capillaries and venules.

A different pattern of blood pressure response was
demonstrated between normal dogs and those dogs with porto-

caval shunts. Autopsy examination at porto-caval shunt dogs demonstrated less marked changes in the liver and the intestine.

Metabolic acidosis was shown to occur and its rate of development was such that it could be buffered by 0.3 mgm. Na H CO_3/kg. in weight/minute of shock.
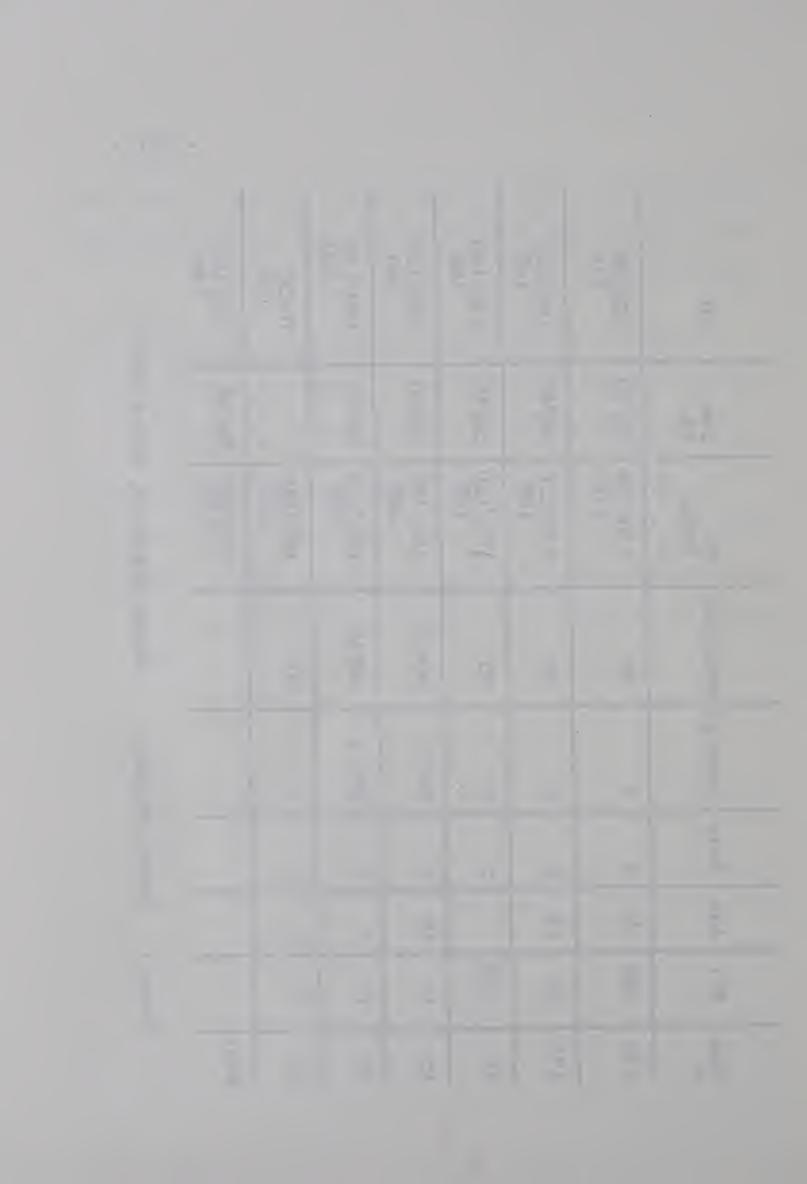
It was shown that successful treatment of all the observed abnormalities occurring during endotoxemia was possible, and that the severely "shocked" animal could be resuscitated for long term survival.

Dog #	Wt.	Age	Endo	Heparin	Nembutal	BP Pulse I	Low Rt.	10
18A	20½	1½	5	2	30	170/130 110	30/20	100/80 115
17A	24	1½	5	2	30	170/110 185	60/40	150/130 145
16	17½		5	2	30	155/110 190	50/40	130/120 140
15	17	1½	5	2+0.5	30+15	160/150 180	90/80	130/120 160
13	17	3	5	2+1.5	30+15	190/150 200	60/50	150/130 150
12	15	4	5	2	30	160/140 170		70/50 130
Avg.						167/132 172	58/46	122/105 140

Group I   Normal Animals   Blood Pressure, Pulse Rate

Dog #	40	1½	2	3	4	5	6	Survival
18A	130/110 145	100/60						15 hrs.
17A	100/80 135	70/50	60/40 140	80/60 140	90/60 165			8 hrs.
16	120/100 165	90/70	120/90 140	130/110 165	130/110 165			Permanent
15	150/140 170		120/100 150	130/120 145	150/130 140			Permanent
13	150/120 190		150/130 190	160/140 180	110/90 210	130/110 200		Permanent
12	140/124 180	100/80 185	100/40 200	130/100 190	140/120 200			10 hrs.
Avg.	132/112 164	90/65	110/90 164	126/106 144	124/102 176	130/110 200		11 hrs.

Group I   Normal Animals   Blood Pressure, Pulse Rate

Dog #	Wt.	Age	Endo	Heparin	Nembutal	Hct I PU	Hct 40 PU	Hct 1½hr PU	I pH	10 pH
11	15		5	2	30	44.4/760		52.3/558		
20C	14	1	5	2	30	48.5/580	53.3/526	51.0/557	7.33	7.34
21C	11	1	5	2	30	37.6/681	56.8/711	48.1/424	7.37	7.38
22C	18½	1½	5	2	30	42.2/1143	45.4/1000	46.0/1000	7.33	7.34
23C			5	2	30	43.6/840	44.3/908	49.3/908	7.38	7.38
24C	24½	4	5	2	30	51.4/1290	49.8/1290	53.3/1160		
Avg.						44.6/949	49.9/887	50.0/768	7.35	7.36

Group II   Normal Animals   Hematocrit, Plasma Volume

pH, pCO_2 total CO_2

Dog #	40 pH	2hrs pH	3hrs pH	4hrs pH	I	pCO_2 / HCO_3 10	40	2hrs	3hrs	4hrs	Survival
11											15 hrs.
20C	7.30	7.36	7.41	7.41	33.5 / 18.0	25.0 / 14.0	13.5 / 6.8	12.3 / 7.1			10 hrs.
21C	7.34	7.30	7.35		28.8 / 16.9	15.0 / 9.1	16.5 / 9.1	15.0 / 7.6	15.7 / 8.9		8 hrs.
22C	7.35	7.16	7.05		27.6 / 14.9	27.5 / 15.2	18.1 / 10.5	19.0 / 7.2	26.5 / 7.9		Permanent
23C	7.30	7.26	7.28	7.42	31.0 / 17.2	26.5 / 15.9	28.5 / 14.4	34.8 / 16.2	25.8 / 12.5	19.0 / 12.6	Permanent
24C											12 hrs.
Avg.	7.32	7.27	7.27	7.41	30.2 / 16.8	23.5 / 13.6	19.2 / 10.2	20.3 / 9.5	22.6 / 9.6	19.0 / 12.6	11 1/4 hrs.

Group II   Normal Animals   Hematocrit, Plasma Volume

pH, pCO_2, total CO_2

Dog #	Weight	Age	Dose of Endo	Heparin	Anest. Nembutal	BP Pulse I	Low Rt.	10
1	10kg.	2yrs.	5mg/k	2mg/k	30mg/k	200/140 180	60/40 78	110/80 98
2	10kg.		5mgm	2mgm	30mg	180/140 180	40/30 150	130/100 150
4	9kg.	2yrs.	5	2	30	185/130 180		140/100 156
5	11kg.		5	2	30	220/140 228	50/40	150/120 150
6	13kg.	1½yrs.	5	2	30+2	160/120 150		80/60 120
7	11kg.	9mos.	5	2	30+9	180/130 180		90/70 115
8	14½kg.		5	2	30	120/80 110		60/30 90
9	10½	6yrs.	5	2	30	140/80 120	160/100 114	85/60 110
10	13½	1yr.	5	2	30+6	170/120 200		160/100 110

Group III   Normal Animals   Blood Pressure, Pulse Rate

Dog #	Weight	Age	Dose of Endo	Heparin	Anest. Nembutal	BP Pulse I	Low Rt.	10
14	11½		5	2	30	180/150 170		60/50 130
19	12½	1½	5	2	30	160/120 140	20/10	70/50 120
20A	11	4	5	2	30+8	160/120 180	50/40	130/100 175
21A	11.5	1	5	2	30+6	160/120 160	40/30	60/40 160
22A	17	1½	5	2	30+7	160/110 195	60/40	130/110 180
23A	21½	1½	5	2	30	190/140 165	40/30 .	120/100 155
24A	23½	1½	5	2	30	170/120 200	30/20	140/120 190
Avg.						170/120 171	55/38 114	108/80 138

Group I·II   Normal Animals   Blood Pressure, Pulse Rate

Dog #	40	1½hrs.	2hrs.	3hrs.	4hrs.	5hrs.	6hrs.	7hrs.	8hrs.
1	100/60 98	75/40 128							
2	160/120 180	100/65 180		100/70 160					
4	110/80 150	50/30 144	80/40						
5	110/70 160	130/100 175	130/100 175		135/100 185				
6	50/40 130	40/30 120			48/40 120	60/48 120		80/60 100	80/70 110
7	70/60 130	76/60			140/108 70		90/70 150	70/50 170	60/40 150
8	65/40 100	45/30 120	60/45 135						
9	80/50 120	45/30 120	45/30 120		45/30 135	70/50 140			100/70 160
10	140/90 140.		130/100 140						

Group III   Normal Animals   Blood Pressure, Pulse Rate

Dog #	40	1½hrs.	2hrs.	3hrs.	4hrs.	5hrs.	6hrs.	7hrs.	8hrs.
14	90/80 155	50/40	60/40 165	70/60 175	80/60 175				100/80 195
19	100/70 130	100/60	90/70	105/85 145	110/95 150				
20A	70/50 135	60/50	60/50 110	70/60 215	90/70 240				
21A	110/80 160	100/75	80/60 160	80/70 185					
22A	90/70 150	50/30	60/40 165	110/80 165					
23A	150/120 165	110/70	110/80 160	150/120 160					
24A	110/90 190								
Avg.	100/73 143	73/51 141	82/59 147	98/78 172	93/72 154	65/49 130	90/70 150	75/55 135	85/65 154

Group III   Normal Animals   Blood Pressure, Pulse Rate

Dog #	Beg pH	10 pH	40 pH	1½ pH	2½-3 pH	3½-4 pH	I pCO$_2$	10 pCO$_2$	40 pCO$_2$	1½ pCO$_2$	2½-3 pCO$_2$	3½-4 pCO$_2$
1	7.42			7.31			33.2			20.2		
2	7.38			7.34			30.5			20.7		
4	7.37			7.28			37.0			23.0		
5	7.34			7.36	7.31		33.7			26.3	30.5	
6	7.33			7.22	Also long Term pH		36.0			21.3		
7	7.32			7.29	Also long Term pH		36.5			21.5		
8	7.35			7.26			37.5			24.5		
9	7.36			7.29	7.27	7.25	43.5			21.4		
10												

Group III   Normal Animals   pH, pCO$_2$, total CO$_2$

Dog #	Beg pH	10 pH	40 pH	1½ pH	2½-3 pH	3½-4 pH	I pCO$_2$	10 pCO$_2$	40 pCO$_2$	1½ pCO$_2$	2½-3 pCO$_2$	3½-4 pCO$_2$
14	7.35	7.36	7.22	7.21	7.26	7.22						
19	7.32	7.19	7.28	7.25	7.29	7.29	37.0	35.0	30.6	25.5	23.5	22.0
20A	7.30	7.25	7.26	7.25	7.34	7.35	38.5	33.4	32.0	22.7	14.7	18.0
21A	7.36	7.33	7.32		7.41	7.41	32.0	26.3	27.5		24.5	21.0
22A	7.31	7.17	7.18	7.22	7.28		28.5	40.0	38.3	37.0	26.5	
23A	7.34	7.32	7.41	7.41	7.41	7.41	14.8	28.0	18.8	21.0	20.0	18.3
24A												
Avg.	7.35	7.27	7.28	7.31	7.32	7.32	33.8	34.5	29.4	23.8	23.3	19.8

Group III   Normal Animals — pH, pCO$_2$, total CO$_2$

Dog #	I Total CO_2	10 Total CO_2	40 Total CO_2	1½ Total CO_2	2½ Total CO_2
1	22.8			10.4	
2	19.2			11.2	
4	21.6			10.9	
5	18.5			16.5	15.7
6	19.0			9.0	
7	19.3			10.6	
8	20.6			11.3	
9	24.9			10.6	
10					

Group III   Normal Animals   pH, pCO_2, total CO_2

Dog #	I Total CO_2	10 Total CO_2	40 Total CO_2	1½ Total CO_2	2½ Total CO_2
14					
19	19.6	14.0	14.9	11.6	11.6
20A	19.5	14.8	14.8	10.2	7.2
21A	18.5	14.2	14.4		15.7
22A	14.8	15.2	15.0	15.7	12.8
23A	8.2	14.8	11.2	13.8	12.6
24A					
Avg.	17.4	14.6	14.1	11.8	12.6

Group III   Normal Animals   pH, pCO_2, total CO_2

Dog #	3½-4 HCO₃	I PU	40 PU	1½ PU	2½ PU	I Hct	40 Hct	1½ Hct	2½ Hct	Survival
1		510		496		45.7		55.0		14½ hrs.
2		482		525		50.0		52.5		Permanent
4		419		489		54.2		48.9		22 hrs.
5		600		600		53.3		51.7		Permanent
6						46.7		54.7		13½ hrs.
7						52.5		65.7		11 hrs.
8		730		653		47.7		55.7		3½ hrs.
9		564		400		38.3		61.6		14 hrs.
10		680		753		45.7		55.6		15 hrs.
14										14½ hrs.
19	10.9	592	458		507	47.1	56.9		64.3	38 hrs.

Group III   Normal Animals   Plasma Volume, Hematocrit

Dog #	3½-4 HCO$_3$	I PU	40 PU	1½ PU	2½ PU	I Hct	40 Hct	1½ Hct	2½ Hct	Survival
20A	10.1	451	631			53.8	59.0			12 hrs.
21A	15.4	653	500		475	39.3	45.3		33.2	15 hrs.
22A		914	711		744	39.3	40.8		51.3	10½ hrs.
23A	13.4	908	750		884	44.4	49.4		50.5	16 hrs.
24A		1020	1240		1050	37.2	48.1		44.3	Permanent
	12.6	656	715	559	732	46.4	49.4	55.7	48.7	17.6

Group III   Normal Animals   Plasma Volume, Hematocrit

Dog #	BP 0	Initial Low	10	40	1 1/2	2	3	4
178	130/90	15/10	35/30	65/55	15/10			
138	150/90	60/30	70/45	95/65	70/40	75/40	75/45	65/30
955	190/110	70/40	100/60	60/30	65/30			
79	130/100	75/50	65/50	110/95	160/135	170/130	185/150	
933	150/70	70/50	105/80	75/60	80/60	85/70	90/80	85/70
A50	150/85	115/60	160/80	210/140	160/100	130/80	130/90	135/95
118	165/125	60/35	85/60	105/90	95/80	105/90	130/110	140/115
916	160/95	100/55	110/60	160/90	105/50	110/85	100/60	115/80
839	135/80	70/30	110/70	115/90	110/75	120/80	130/70	95/70
664	165/140	35/25	80/50	130/95	85/75	90/85	120/100	120/95
88	150/110	60/30	65/35	85/45	90/55	90/55	95/65	110/70
89	160/130	65/50	70/30	80/30	95/65	90/70	95/75	105/95
Average	142/101	67/39	86/54	106/75	94/65	103/76	108/81	105/79

Group IV   Normal Animals   Blood Pressure

Dog #	5	6	8	10	12	Defecation	Untreated Survival
178						2W	1 1/2 hrs.
138						2N	4 3/4 hrs.
955						1N-1B	2 hrs.
79						3W-sl.B.	
933	65/50	80/60	75/50	80/60	65/50	7W-15B	12 hrs.
A50	220/140					2N-3W-2B	6 hrs.
118	120/95	130/95	130/105	110/75	105/70	1N-2W-4M-2B	26 hrs.
916	110/75	120/60				3W-sl.B.	7 1/4 hrs.
839	75/50					2N-7W	5 1/2 hrs.
664	150/?	90/?	110/?	110/?	115/?	1N-2W-2B	26 hrs.
88							
89							
Average	123/82	103/70	110/88	105/72	95/60		10 1/2 hrs.

Group IV   Normal Animals   Blood Pressure

Dog #	BP 0	Initial Low	10	40	1 1/2	2	3
955	170/100	40/50	70/50	16/12	13/9		
916	105/70	40/25	65/45	85/60	45/30	45/30	50/35
118	125/105	30/25	12/8	16/8	20/12	20/12	20/11
A50	90/60	20/10	55/20	40/30			
933	120/70	30/25	70/55	18/15	25/19	22/20	7/4
79	75/70	25/?	25/?	40/?	25/?	22/?	32/?
Average	114/81	31/27	49/39	36/25	29/10	27/21	27/16

Group IV   Normal Animals   Femoral Marrow Pressures

Dog #	4	5	6	8	10	12
955						
916	21/17	14/10	13/10			
118	22/19	22/20	23/21	17/10	4/2	
A50						
933	21/20	19/17	20/19	19/?	22/21	8/?
79						
Average	21/19	18/16	19/13	18/10	13/11	8/?

Group IV   Normal Animals   Femoral Marrow Pressures

Dog #	BP 0	Initial Low	10	40	1 1/2	2	3
959	130/90	100/30	90/30	120/?	105/?	115/?	110/65
640	140/95	110/90	120/95	105/75	90/60	110/70	95/60
Pharoah	135/110	70/60	65/50	80/65	55/45	55/50	60/50
921	130/90	115/60	120/90	125/90	125/90	130/95	130/100
72	180/120		115/70	150/110	155/110	155/115	
503	180/90	110/45	130/100	90/70	90/75	110/70	130/75
957	150/110	110/90	160/120	110/70	90/40	90/50	70/?
Average	149/101	102/62	114/79	111/80	101/70	109/73	99/70

Group V   Porto-Caval Shunt Animals   Blood Pressure

Dog #	4	5	6	8	10	12
959	100/55	105/70	105/55			
640	135/90	80/60	115/75	115/70	105/80	90/70
Pharoah	105/80					
921	90/60	100/60	90/60	120/80	105/75	110/70
72	135/85			145/105	140/100	145/110
503	95/65	165/125	200/85			
957	65/?					
Average	109/72	112/79	127/69	127/85	117/85	115/83

Group V   Porto-Caval Shunt Animals   Blood Pressure

Dog #	13	15	16 1/2	16 3/4
959				
640	95/75	105/80	140/130	65/55
Pharoah				
921	110/65			
72	130/105			
503				
957				
Average	112/82	105/80	140/130	65/55

Group V   Porto-Caval Shunt Animals

Blood Pressure

Dog #	BP 0	Initial Low	10	40	1 1/2	2	3	4	5
959	56	30	45	35/22	35	20	8	8	12
640	50/40	35/30	62/58	37/30	20/18	22/20	9/8	20/18	8
Pharoah	105/80	35/32	26/22	70/55	40/35	35/30	35/28		
921	45/20	8/6	16/13	12/8	8/4	6/4	6/5	5/4	4
Avg.	51/47	27/23	37/31	38/29	26/19	21/18	14/13	11/10	8

Dog #	6	8	10	12	13	15	16 1/2	16 3/4
959	8							
640	13/11	16/12	4	8	9	10	4	4
Pharoah								
921	7	6	4	4	0		4	4
Avg.	9	11	4	6	4	10	4	4

Group V   Porto-Caval Shunt Animals   Femoral Marrow Pressures

Dog #	0 BP	I.Low BP	10 BP	40 BP	1½hrs BP	2hrs BP	Pre-Rx BP
957	150/100	110/90	160/120	110/70	90/40	90/50	65/?
959	130/90	100/30	90/30	120/?	105/?	115/?	105/55
9	130/85	60/30	85/70	105/85		75/55	70/60
47	110/90	40/30	60/50	85/75	75/65	70/65	55/50
178	130/90	15/10	35/30	65/55	15/10		15/10
139							
Avg.	130/91	65/38	86/60	97/71	71/38	88/56	62/44

Group VII   Normal Dogs   pH,pCO$_2$, total CO$_2$

Lactate, Pyruvate

Dog #	O pH	Pre Rx pH	O pCO_2	Pre Rx pCO_2	O Total CO_2	Pre Rx Total CO_2	O $NaHCO_3$	Pre Rx $NaHCO_3$
957	7.35	7.32	21.0	15.0	11.8	7.9	11.2	7.5
959	7.33	7.25	26.5	16.2	14.2	7.5	13.4	7.0
9	7.34	7.25	31.0	29.7	17.0	13.5	16.1	12.6
47	7.22	7.18	32.5	19.1	14.2	7.5	13.2	6.9
178	7.39	7.20	23.7	15.1	14.7	7.0	14.0	6.0
139	7.35	7.33	32.0	19.2	18.0	10.4	17.0	9.8
Avg.	7.33	7.26	27.8	19.0	14.9	9.0	14.2	8.3

Group VII   Normal Dogs   pH, pCO_2, total CO_2

Lactate, Pyruvate

Dog #	O Lactate	Pre Rx Lactate	Post Rx Lactate	24 hrs. Lactate
957	11.93	19.3		13.2
959	6.01			22.5
9	15.65	22.4	27.7	36.3
47	5.56	56.2	56.7	17.65
178	21.20	61.2	77.1	
139	22.5	68.9	52.9	
Avg.	13.8	38.0	53.6	22.4

Group VII   Normal Dogs   pH, pCO$_2$, total CO$_2$

Lactate, Pyruvate

Dog #	O Pyruvate	Pre Rx Pyruvate	Post Rx Pyruvate	24 hrs. Pyruvate	# Hours to Rx
957	1.03	1.65		1.44	3 1/2
959	1.46	2.77	4.57	1.59	6 1/3
9	0.83	1.79	1.99	2.08	4
47	1.11	3.26	3.40	2.62	3 1/2
178	0.77	2.79	3.96		1 1/2
139	1.74	4.05	3.45		6
Avg.	1.14	2.72	3.37	1.96	4

Group VII   Normal Dogs   pH, pCO$_2$, total CO$_2$

Lactate, Pyruvate

Dog #	O pH	Pre-Rx pH	Post-Rx pH	Final pH	O pCO$_2$	Pre-Rx pCO$_2$	Post-Rx pCO$_2$	Final pCO$_2$
959	7.33	7.25	7.38	7.25	26.5	16.2	18.0	25.0
957	7.35	7.32			21.0	15.0		
72	7.40	7.32	7.25	7.33	25.4	20.2	17.7	22.0
138	7.34	7.17	7.26		25.0	12.8	20.5	
139	7.35	7.33	7.31	7.26	32.0	19.2	24.9	26.8
178	7.39	7.20	7.12	7.21	23.7	15.1	27.0	15.6
47	7.22	7.18			32.5	19.1		
965	7.38	7.26	7.28		29.5	10.0	18.4	
9	7.34	7.25	7.26	7.07	31.0	29.7	39.5	46.6
79	7.37	7.37	7.37	7.35	22.5	16.0	21.5	18.4
Avg.	7.35	7.26	7.28	7.24	26.9	17.3	23.4	25.7

Group VIII   Normal and Porto-Caval
Shunt Animals

Effect of Treatment
on Buffer Reserve

Dog #	0 Total CO_2	Pre-Rx Total CO_2	Post-Rx Total CO_2	Final Total CO_2	0 $NaHCO_3$	Pre-Rx $NaHCO_3$
959	14.2	7.5	10.9	11.4	13.4	7.0
957	11.8	7.9			11.2	7.5
72	16.0	10.8	8.1	11.6	15.2	10.2
138	13.8	5.0	9.4		13.0	5.0
139	18.0	10.4	12.9	12.5	17.0	9.8
178	14.7	7.0	9.3	6.5	14.0	6.0
47	14.2	7.5			13.2	6.9
965	17.7	7.0	9.0		16.8	6.0
9	17.0	13.5	18.2	14.5	16.1	12.6
79	13.3	9.5	12.6	10.4	12.6	9.0
Avg.	15.1	8.6	11.3	11.2	14.2	8.0

Group VIII   Normal and Porto-Caval   Effect of Treatment

Shunt Animals   on Buffer Reserve

Dog #	Post-Rx NaHCO$_3$	Final NaHCO$_3$	Pre-Rx Length	Survival
959	10.4	10.6	6 1/3 hrs.	5 days- 2 hrs.
957			3 1/2 hrs.	20 days- 4 hrs.
72	7.6	11.0	13 hrs.	13 hrs.
138	8.8		4 1/4 hrs.	3 1/2 hrs.
139	12.1	11.7	6 hrs.	11 3/4 hrs.
178	8.5	6.0	1 1/2 hrs.	24 3/4 hrs.
47			3 1/2 hrs.	24 1/2 hrs.
965	8.4		10 3/4 hrs.	4 1/4 hrs.
9	17.0	13.1	4 hrs.	22 days
79	12.0	9.8	25 1/2 hrs.	3 1/2 days
Avg.	10.6	10.4	8 hrs.	

Group VIII   Normal and Porto-Caval   Effect of Treatment
              Shunt Animals   on Buffer Reserve

Dog #	Urine Return	BM Post	Effect of Treatment
959	1 hr. 2 min.	2W	Overwhelming Infection (Antibiotic stopped in 48 hours)
957	3 hrs.	0	Metastatic deposits of Infection- (Antibiotics stopped in 1 week)
72	0	1B	Hypovolemia
138	2 3/4 hrs.	2W	Hypovolemia
139	1 3/4 hrs.	7B	Continued Hemorrhage from intestine and operative wound site
178	5 1/2 hrs.	2W-3B	Hypovolemia (Dog had diarrhea prior to shock)
47	0	1B	Vomited, aspirated and died of asphyxia
965	0	3B	Cardiac Failure
9	5 hrs.	2W	Metastatic foci of infection (Anti-biotics stopped in 1 week)
79	?	?	Diffuse overwhelming pneumonia (Antibiotics stopped in 36 hours)

Group VIII   Normal and Porto-Caval   Effect of Treatment

Shunt Animals   Buffer Reserve

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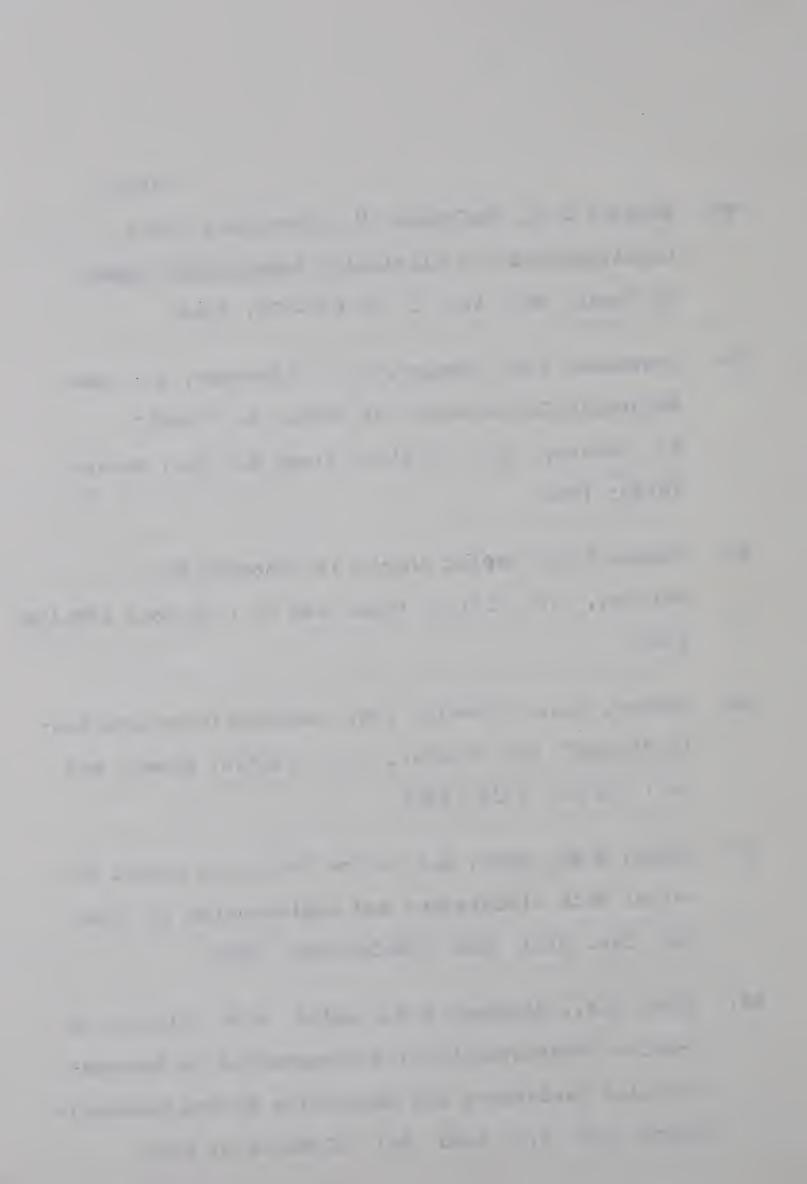   Biol. Med. 115:833-837: 1964

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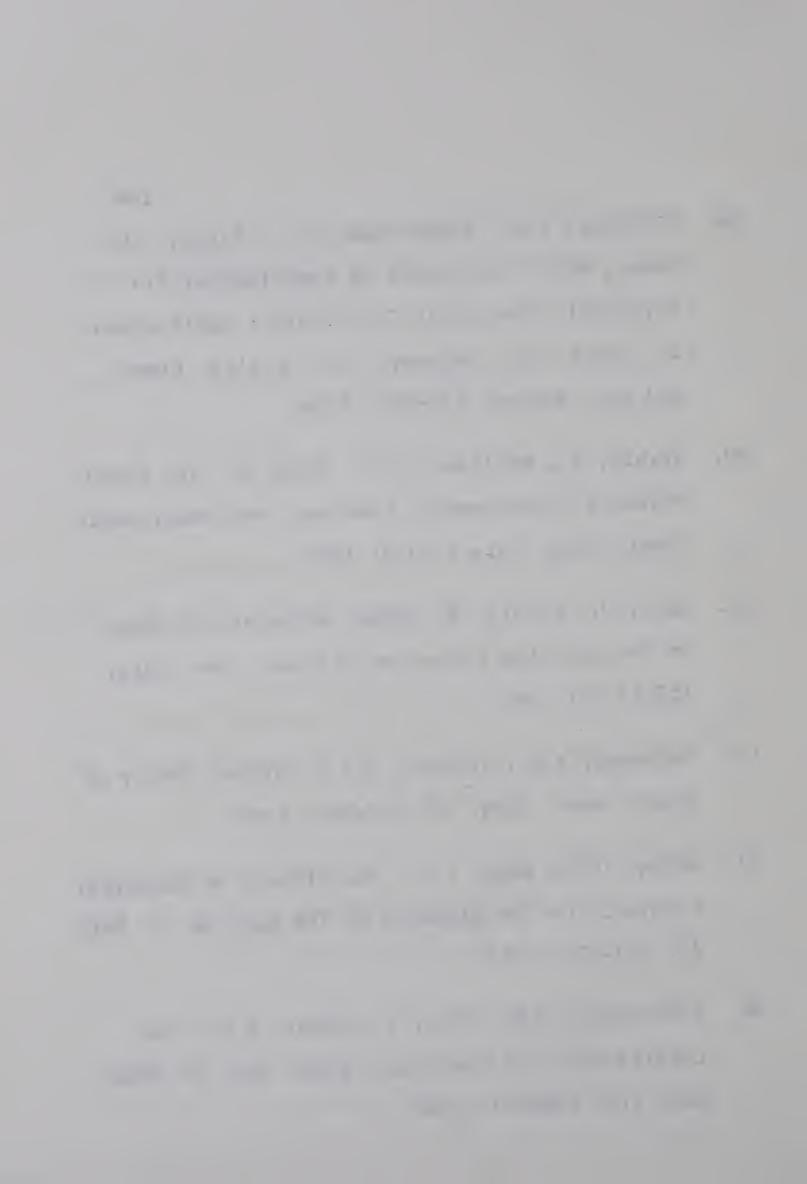Hershey, S.G.: Little Brown and Co.: Boston: 129-138;
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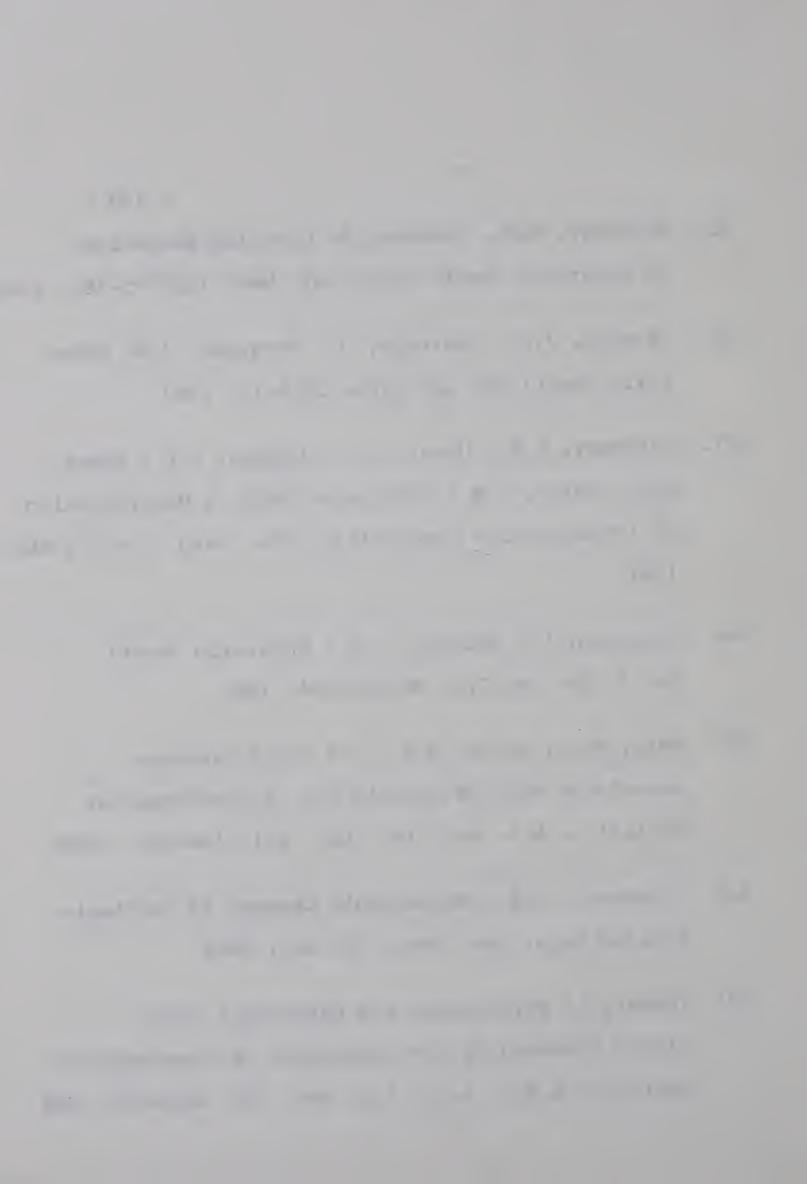Shock: Ann. N.Y. Acad. Sci. 92:662-670: 1961

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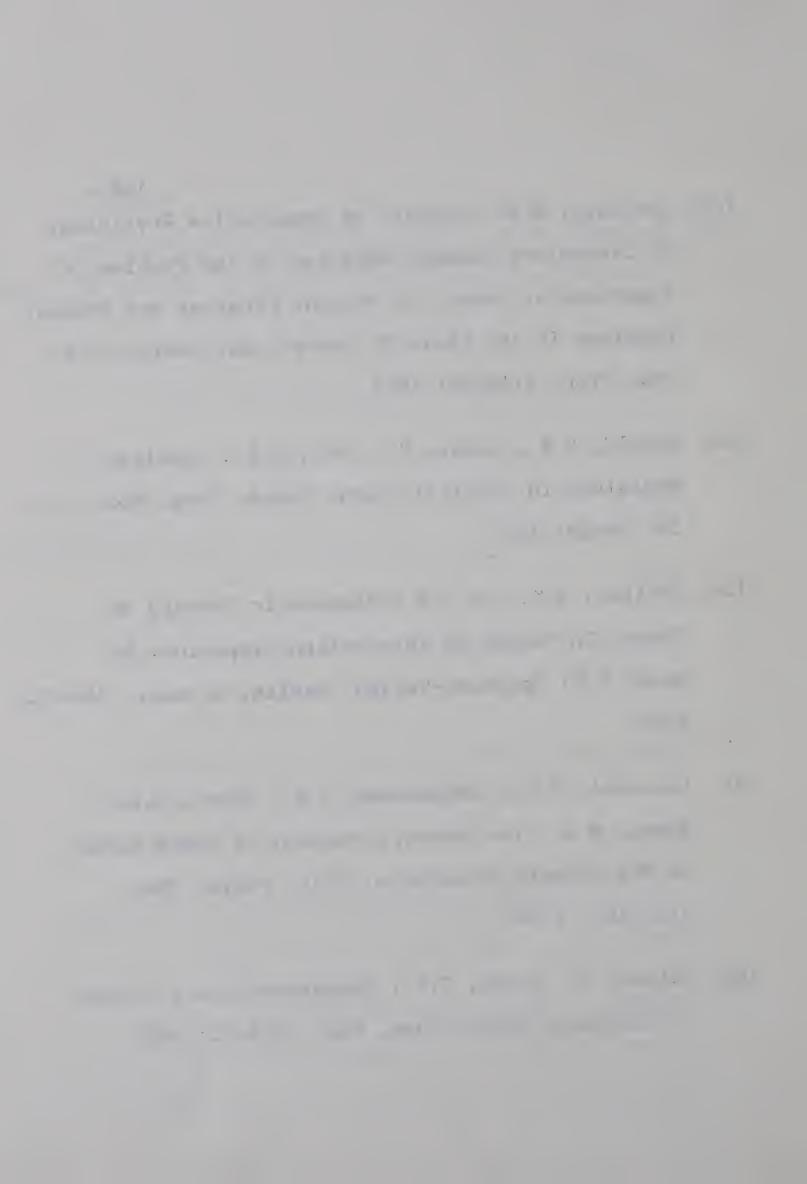   Localization of Endotoxin: Proc. Soc. Ex. Biol.
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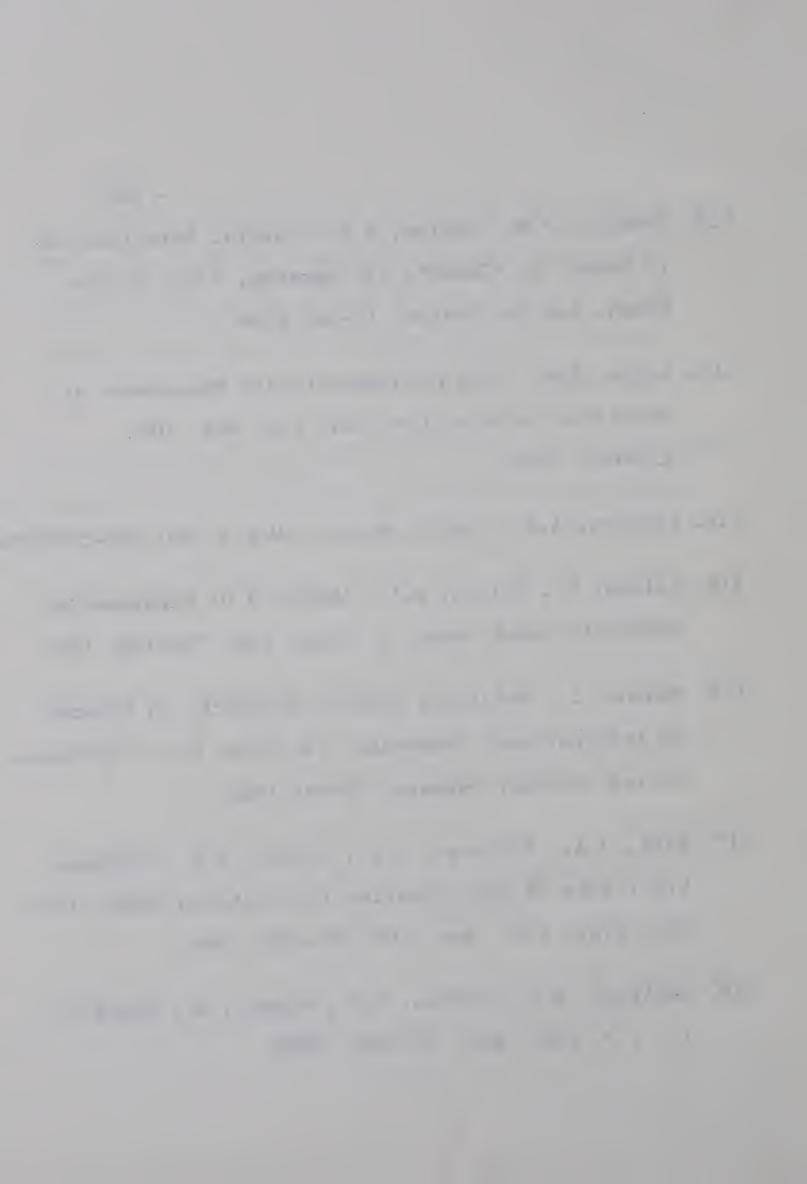
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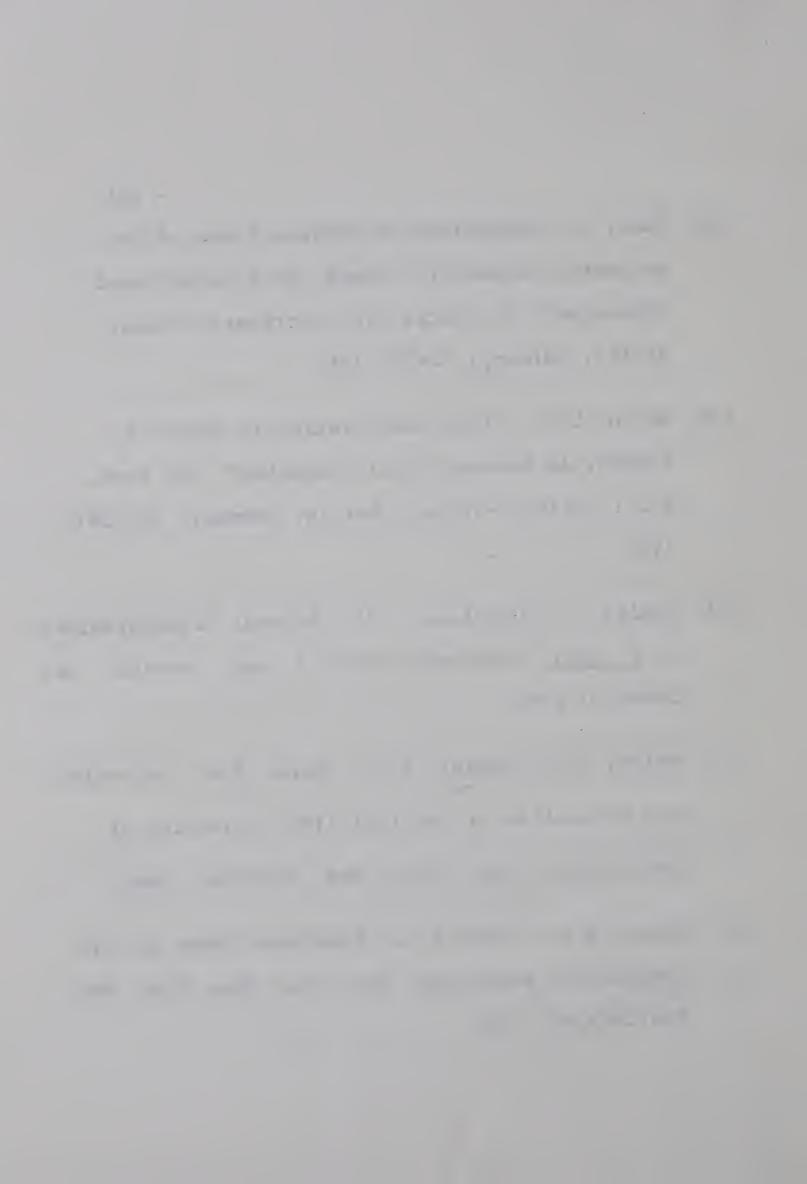   Soc. Expt. Biol. Med. 109: 200-202: 1962

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